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DANIÆ, FENNIÆ, NORVEGIÆ ET SUECIÆ

VOL. 36 DECEMBER 1951 FASC. 6

CHEMOTHERAPY OF CANCER[1]

by

Jørgen Bichel

The ideal *chemotherapeutic agent* in the treatment of cancer would be a substance which on administration to the affected organism destroyed all malignant cells without causing damage to its normal constituents.

Such a substance is unknown, and so far it is impossible to cure any case of cancer chemotherapeutically (the direct application to tumors of chemicals with a local and often caustic effect cannot be termed chemotherapy in the proper sense of the word).

The following survey will be confined to such antineoplastic chemicals as are supposed to exert a direct action on cancer cells. The treatment of cancer by endocrine means will not be discussed. Whether hormonal treatment of cancer may be called chemotherapy depends on the definition of this word. The hormones accentuate effects normally exerted in the organism, and their action in cancer is probably not a result of a direct action on the cancer cell but is brought about by an alteration in its environment.

Chemotherapy of cancer is not a new field of medicine. However, it is only during the last decade that substances have been found which possess tumor-inhibiting properties sufficiently pronounced to be of any therapeutic value. The effect of such substances is only palliative, and the indications are limited to certain types of tumors, especially generalized hyperplastic disorders of the hematopoietic tissues, such as leukemias, Hodgkin's disease, reticulolymphosarcomatosis, etc., in which radical surgery or local irradiation is impossible.

[1] Aided by grants from the Lady Tata Memorial Trust, Anders Hasselbalch's Anti-Leukemia Foundation, and C. P. Schepler and Wife's Bequest, the Irma Foundation. Read before the 17th Congress of the Northern Association for Medical Radiology at Aarhus, June 1951; submitted for publication, June 18, 1951.

From the Clinical Department and the Research Laboratories, the Radium Centre for Jutland (Director: Professor Carl Krebs), University of Aarhus, Denmark.

All antineoplastic chemotherapeutic agents known today are cytotoxic substances, which damage all cells whether normal or malignant. Their effect is unspecific, resulting in the destruction of the cells, but their mode of action may somewhat differ. That these cytotoxic chemicals may, nevertheless, be of some value in tumor therapy, is due partly to the high vulnerability of cancer cells to all sorts of damaging influence, and partly to the accentuated effect which these substances exert on rapidly proliferating cells. If, however, the difference in vulnerability of normal and malignant cells were very wide, it should still be possible to destroy all malignant cells by means of cytotoxic chemicals administered in suitable concentrations without causing irreparable damage to the normal tissues. This is, however, not so. A malignant tumor consists of cells with varying degrees of resistance and will invariably contain cells which are more resistant than some of the more sensitive normal cells. The destrution of all malignant cells in an organism would require such heavy concentrations of cytotoxic substances that survival of the host would be impossible. It would be especially the rapidly proliferating cells of the blood-forming organs which would be damaged and an aplastic anemia would result.

It is known from experiments that it is possible to kill all leukemic cells in a leukemic mouse by means of the nitrogen mustards but the dose required is of the order of 10—20 times that which can be tolerated by the mouse (35).

In order to clarify the present-day position of the chemotherapy of cancer and to form some idea of what we can expect of the future on the basis of our present knowledge, or perhaps, rather what we cannot expect, it may be useful to compare the mode of action of the tumor-inhibiting chemicals with that of the drugs used in microbial infections.

The chemotherapy of microbial infections is based upon the differences which exist between the chemical constitution and vital metabolic processes of bacterial cells and those of the cells of the host. This makes it possible to interfere with vital processes of the micro-organisms without causing damage to the cells of the infected host.

The precise differences between cancer cells and normal cells are unknown. It is appreciated that the cancer cell differs from the normal cell in certain fundamental qualities. This is manifested, above all, in the uninhibited growth of the cancer cells in the organism. It is but natural to assume that the changed behavior of cancer cells must have its origin in, or anyhow be accompanied by qualitative changes of, the chemical constitution or metabolic processes of the cells.

But in spite of an enormous amount of research work it has never been possible to demonstrate, with certainty, any chemical difference between cancer cells and normal cells. Such differences as have been

found are of a quantitative nature. Generally, the structure of cancer cells will approach that of normal undifferentiated cells. This has been shown particularly with regard to their enzymatic pattern (26).

If we knew the chemical differences, we should be able to search for chemotherapeutic agents against cancer on a far more rational basis than has hitherto been possible.

There is another very essential difference between the possibilities of antineoplastic and antimicrobial chemotherapy. The sulfa drugs and the modern antibiotics are bacteriostatic, *i. e.*, they may inhibit the multiplication of the bacterial cells without killing them. This will often render it possible for the infected organism to build up its defence, to produce antibodies and combat the infection. The antineoplastic chemotherapeutic substances are also to some degree cytostatic and inhibit the multiplication of the malignant cells. This is, however, not of very great value, as the organism is incapable of producing antibodies against its own tumor cells. There is no immunological difference between the cancer cells and the cells of the organism from which the cancer has its origin. — These facts do not make the prospects for the future any brighter.

Cytotoxic substances kill malignant cells. We do not know any chemical which will convert a malignant into a normal cell; it is characteristic of malignancy that the potentiality of the malignant cells to differentiate, to mature into more specialized cells, is diminished or completely abolished. Nor do we know of any chemical which is able to influence the differentiation of the cells. The highly differentiated specialized cells are often unable to divide mitotically and, thus, a substance which could accelerate differentiation might be of value in the chemotherapy of cancer.

As already pointed out, the antineoplastic chemotherapeutic agents are cytotoxic substances possessing cytostatic and cytocidal properties. They bring about the death of the cells. The end-results of the effects of the different substances are identical, but there are, nevertheless, certain differences in their mode of action.

Several attempts have been made to classify cytotoxic substances into groups according to their mode of action on cells. But great confusion prevails within this field, due, in part, to divergent interpretations of the observations made. All these substances will sooner or later produce observable alterations in the mitotic figures and are, hence, often collectively spoken of as »mitotic poisons». This is, however, hardly justifiable as the observable abnormalities in the mitotic picture are only occasionally direct results of an action on a structure, which is specific for mitosis. In my opinion, the clearest definitions have been given by HADDOW and his collaborators at the Chester Beatty Research

Institute, London, where the cytological effects of the different compounds have been studied for many years. They have suggested that the use of the term »mitotic poison» should be limited to substances such as colchicine, which interfere with a component which is specific for mitosis (38). When colchicine in appropriate concentrations is added to living cells, *e. g.*, in tissue cultures of fibroblasts, the dividing cells will be arrested at metaphase, and it is supposed that this inhibition is due to a defective formation of the mitotic spindle (39). This group of substances has been of very little value in cancer therapy. The arrest at metaphase produced by colchicine in low concentrations seems to be of too short a duration to cause an effective destruction of the cells. However, at higher concentrations, colchicine will produce hemorrhages in tumors and some inhibition of growth, although the general toxic effects of the substance will be too marked (40).

Another group of cytotoxic substances having a cytological effect resembling that of ionizing radiation are known as *radiomimetic* substances. Mustard gas and the therapeutically used nitrogen mustards belong to this group.

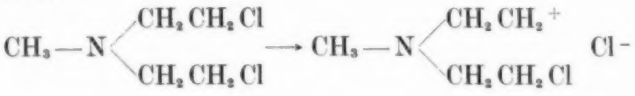
The effects which are exerted by these radiomimetic substances on the cells manifest themselves in abnormalities in the mitotic figures (3, 4). It is supposed that the nitrogen mustards act on the resting nucleus of the cell. The results will become apparent in the form of numerous abnormalities in the chromosomes when the cell subsequently enters mitosis. This action interferes with the genetic material of the cell. It must be stressed that the changes induced in the cells in this way are irreversible and hereditary and may be regarded as mutations. The effects are brought about by very low concentrations of radiomimetic substances. In higher concentrations, the nitrogen mustards have also unspecific cytotoxic properties.

The interaction between the radiomimetic substances and the chromatin of the cell nuclei probably occurs instantaneously. When, for example, nitrogen mustards are injected intravenously, they will not be present in active form a few minutes later in the blood stream (5, 16).

Without entering into the details of the chemistry and the experimental and theoretical premises, I shall briefly mention how these substances are supposed to act.

The most commonly used nitrogen mustard is methyl-bis (β-chloroethyl)amine (HN2).

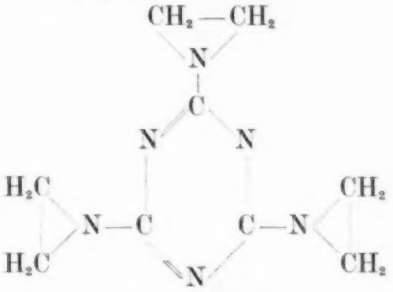
In aqueous solution HN2 will be ionized and a positive carbonium ion be formed:



It is supposed that the second halogen may also be liberated and the carbonium ion is bifunctional, possessing two alkylating groups. It is thought by the English school that these two groups are responsible for the radiomimetic effect. Reacting with acid molecules or groups, they may possibly establish a »cross-linkage» between protein or nucleoprotein molecules in the chromosomes. Furthermore, it has been found that the tendency to chromosome breakage in cells which have been under the influence of HN2 is limited to certain regions of the chromosomes corresponding to the heterochromatin, which in the resting nucleus contains a large amount of nucleic acid (24, 38).

Other substances possessing similar properties are known, *e. g.*, a number of di-epoxides investigated by HADDOW and collaborators.

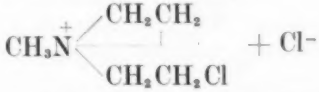
Triethylene melamine also



2—4—6-triethylenimino-s-triazine
TEM.

seems to be radiomimetic. This substance has been used therapeutically at the Sloan-Kettering Institute (33, 46) and has also been given a clinical trial at the Radium Centre for Jutland at Aarhus, as reported by Dr. BJERRE HANSEN.

It should be mentioned that the cross-linkage theory is not universally accepted (2, 32, 50). It has been found that monofunctional nitrogen mustards containing only one reactive group may also be mutagenic, while this property has not been observed in other bifunctional mustard types, which according to the cross-linkage theory should possess it. The biological effect is then supposed to be attached to the formation of highly reactive iminium ions, *e. g.*:



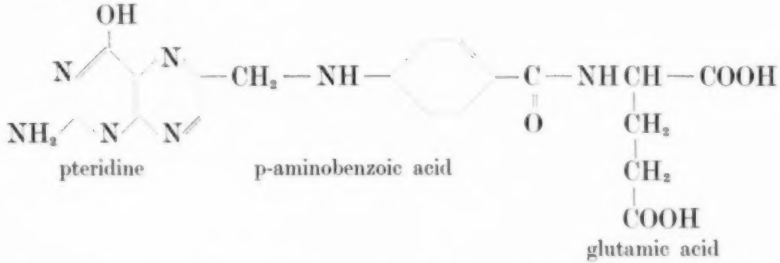
That such an intramolecular transformation takes place in aqueous solution has been pointed out by GILMAN and PHILIPS (24).

However, it seems justifiable to speak of radiomimetic substances, as they act on the resting nucleus, produce irreversible hereditary changes in the cells, are mutagenic and have also been shown to be carcinogenic.

As distinct from the truly radiomimetic cell poisons there are a number of other cytotoxic substances, which with more or less justification have been termed mitotic poisons. Among these, a few have proved to be of therapeutic importance. Urethane, arsenite, certain quinones, etc., which are all highly toxic compounds, belong to this heterogeneous group. They may produce different abnormalities in the mitotic process, even chromosome fragmentation. This is supposed to be due to a stickiness of the chromosomes and should be distinguished from the type of breakage produced in the resting nucleus by radiation and truly radiomimetic substances. The mode of action of some of these substances is reported by Dr. BASTRUP-MADSEN.

It is reasonable to consider the so-called folic acid antagonists separately. They are, it is true, also cytotoxic substances, but since they presumably differ in their mechanism of action from the other substances which I have so far dealt with, and since we know, or believe that we know, something about their mode of action, it may be justifiable to discuss them in some detail.

What we at present understand by folic acid is pteroylglutamic acid (PGA):



As will be seen from the formula, PGA consists of three components, p-aminobenzoic acid, glutamic acid and a pteridine nucleus. Folic acid is pteroylmonoglutamic acid, but folic acid conjugates containing two or more molecules of glutamic acid are also known.

In 1944 it was reported that the *Lactobacillus casei factor* (chemically pteroyltriglutamic acid) would inhibit the growth of certain animal tumors (37). Pteroyltriglutamic acid (teropterin) and pteroyldiglutamic acid (diopterin) have since been investigated as to their tumor-inhibiting properties, both in animal experiments and in human cancer cases, but no definite effect has been obtained (51). It was, however, observed (21)

that these substances had an exacerbating influence on leukemia in children (»acceleration phenomenon»). It has since been found that pteroylmonoglutamic acid (PGA) may also in certain cases accelerate the progression of leukemia both in children and adults (9, 10, 30). The mechanism by which this acceleration phenomenon is brought about is obscure. It occurs in by no means all cases of leukemia.

It has been shown (7) that immature leukemic leukocytes contain more PGA than normal leukocytes, and it has consequently been suggested that leukemic cells should require more PGA for their proliferation than is available in the organism and therefore would show more vivid proliferation after additional administration. The highest content of PGA was found in immature cells from cases of stem-cell leukemia, and it is especially in such cases that a good effect may be expected from administration of folic acid antagonists. However, the conditions here are as yet unsettled. In this connection it may be of some theoretical interest that p-amino-benzoic acid, which is a component part of the PGA molecule, may also cause a similar acceleration of human leukemia when given in small doses (9, 12, 23), an effect which is antagonized by the sulfa drugs. In heavy dosage, p-aminobenzoic acid will depress the leukemic leukopoiesis; attempts have been made to utilize this depression therapeutically, but apparently no real benefits have been obtained (41, 53).

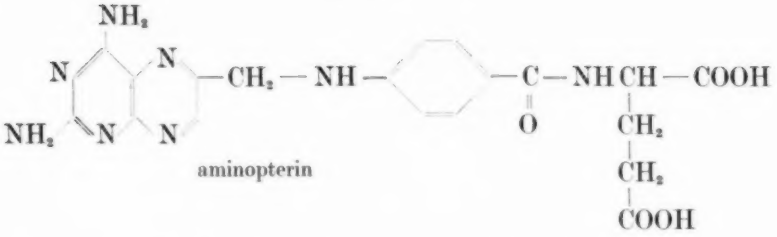
From animal experiments it was known that a diet deficient in PGA could cause bone-marrow aplasia. It was therefore but natural to try to bring patients suffering from acute leukemia into a state of PGA deficiency in order, if possible, to induce an inhibition of the leukemic processes. As it is very difficult to compose an otherwise sufficient diet for human beings deficient in PGA, a different method was adopted, viz. by administration of the so-called folic acid antagonists.

PGA is a growth factor, an essential metabolite, for various microorganisms, and attempts to produce antimetabolites by a re-arrangement of the PGA molecule have been made. By now a number of different PGA antagonists have been produced and some have been tested in the treatment of human leukemia.

The best known of the PGA antagonists is *aminopterin*, which is chemically 4-aminopteroylglutamic acid. This antagonist has been produced by the replacement of a hydroxyl group by an amino group in the PGA molecule.

Like other PGA antagonists, aminopterin is manufactured by the Lederle Laboratories in the U. S. A. It is not yet commercially available, but has been generously supplied for investigational purposes.[1]

[1] Aminopterin and other folic acid antagonists as well as citrovorum factor (Leucovorin) have been placed at our disposal by the Lederle Laboratories (American Cyanamid Company).



aminopterin

Given in suitable doses to experimental animals, aminopterin is capable of producing a state resembling that of PGA deficiency (30, 44), and this state may, at least partially, be overcome by large doses of PGA.

However, severe toxic effects produced by aminopterin cannot be completely neutralized by PGA. It has recently been found that this is, however, possible by another growth factor, the *citrovorum factor* or *folinic acid*, which is required for the growth of *Leuconostoc citrovorum*. PGA may possibly be converted into this substance in the organism (14, 47, 48).

Aminopterin has been tested in the therapy of leukemia during the last three years, and by now it is possible to form an idea as to its therapeutical potentialities. It should at once be pointed out that in no case has a cure been obtained, and that aminopterin is only of very limited value in chronic leukemias (17, 20, 21, 42, 43).

It is, however, beyond doubt that in certain cases of acute leukemia, particularly in children, aminopterin is capable of producing a complete, although only temporary return to normal of the blood and bone marrow and a disappearance of all signs and symptoms. In some other cases the drug may induce incomplete remissions, by which the lives of the leukemic patients are prolonged.

Various difficulties have been encountered in assessing the effect of aminopterin. Spontaneous remissions, especially in children, are not at all uncommon. Moreover, when aminopterin was first used therapeutically, many other measures were often taken simultaneously to keep the patients alive; they were given antibiotics as well as many more blood transfusions than they would otherwise have received, and it is now known that transfusions alone will increase the number of »spontaneous» remissions (6, 19). The number of spontaneous remissions in children and adults with acute leukemia was discussed at a conference on folic acid antagonists held in Boston in January 1949 (17). The statements were somewhat divergent, and I shall not embark upon the subject here. Suffice it to say that it seems evident »that therapy with folic acid antagonists resulted in a much higher remission rate in acute leukemia than

would be expected from the natural history of the disease or experienced with other forms of therapy».

At the Radium Centre at Aarhus we have treated more than 30 cases, but our material cannot be used for an evaluation of the effect of aminopterin, inter alia, because we have studied the combined effect of aminopterin and other chemotherapeutic agents. But we have seen some impressive remissions of up to one year's duration. The following report is an illustrative case of successful aminopterin treatment.

Case Report

A woman, aged 28, was admitted to the Radium Centre for Jutland on July 30, 1949, with a history of angina, stomatitis and a high fluctuating fever of 4 weeks' duration. During the week prior to admission she had also suffered from headache, nausea, vomiting, migratory joint pains and profuse vaginal bleeding.

On admission she was in a very toxic condition. The lymph nodes were not enlarged, but the spleen extended 7—8 cm below the costal margin. Hb. 47 %; RBC 1,500,000;

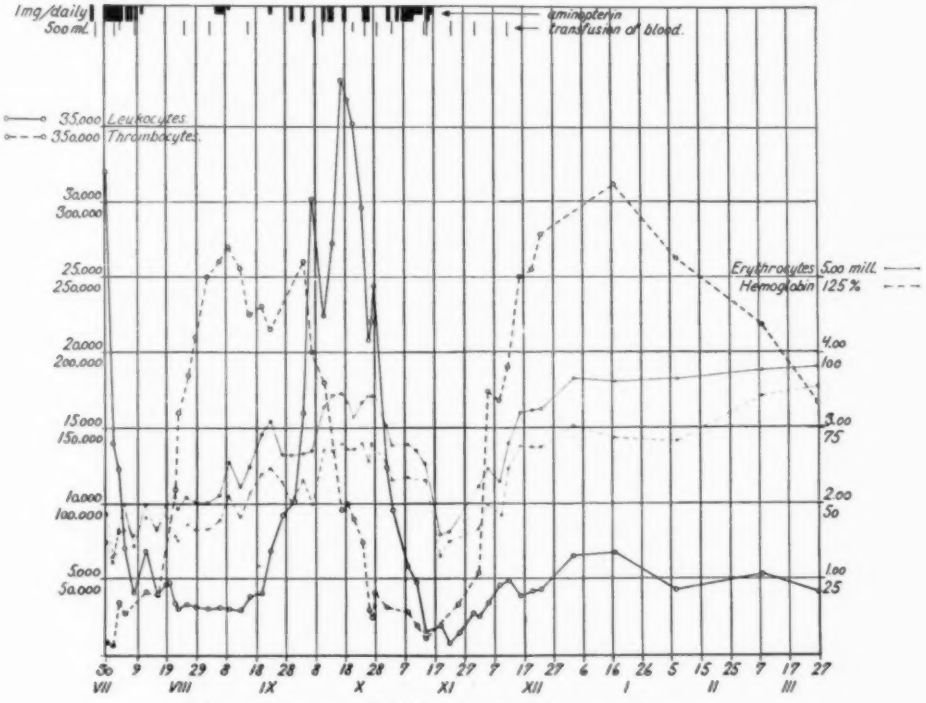


Diagram. Stem-cell leukemia. Female, aged 28 years.

WBC 32,000; thrombocytes 9,000. The differential count revealed 97 % monocytoid blast forms. The bone marrow was abundant in cells with about 80 % blasts.

The course of the disease is seen from the diagram. Penicillin, and later streptomycin, transfusions, and aminopterin were given. An abrupt fall in the white count occurred, and the hemoglobin level and erythrocyte count began to increase, and what was more important, the number of thrombocytes rose to normal values. The patient improved: the temperature returned to normal, and the spleen decreased in size. In September the patient was discharged without symptoms, but by the beginning of October she was re-admitted, with epistaxis, angina, stomato-gingivitis and fever. She was again given antibiotics, blood transfusions and aminopterin, but gradually her condition apparently became absolutely hopeless. However, a further remission set in at the beginning of November; her condition improved rapidly, and in December she was completely symptom-free. Differential counts of blood smears and bone marrow were normal; the spleen could not be palpated, and she felt completely well.

Table 1

Bone-marrow counts

It appears that the first remission (August 1949) was only partial. The second remission (December 1949) was, however, complete. Marrow smears from January 1950 were essentially normal.

	July 27 1949	Aug. 23 1949	Aug. 31 1949	Nov. 3 1949	Nov. 10 1949	Jan. 17 1950
Blasts	82.0	3.0	4.0	10.0	6.0	3.0
Promyelocytes	8.5	6.0	9.0	74.5	25.0	4.0
Myelocytes neutr.	4.0	42.0	26.0	5.5	33.5	16.0
Myelocytes eos.			0.5	0.5		2.5
Myelocytes bas.						0.5
Metamyelocytes	2.0	15.5	24.5	2.5	13.5	13.0
Band forms	0.5	5.0	3.5		1.5	6.5
Polymorph. leuk. neutr.	1.0	11.0	15.5	1.0	4.0	15.0
Polymorph. leuk. eos.					0.5	2.5
Lymphocytes	1.0	3.5	5.0	3.5	12.5	7.0
Monocytes		1.5	1.0	1.0	1.0	0.5
Plasma cells			2.0			1.5
Proerythroblasts		0.5	0.5			
Bas. erythroblasts				0.5	1.5	1.0
Polychr. erythroblasts		5.0	1.5			14.5
Ortochr. erythroblasts	1.6	6.5	7.0	1.0	1.0	12.0
Megacaryocytes						
Reticulum cells						0.5
Unidentified		0.5				

In March 1950 she became pregnant. At that time the picture of the peripheral blood was normal. S. R. 8 mm/1 hour; Hb. 86 %; RBC 3,780,000; platelets 219,000. Differential count: polymorphs, neutr. 50, eos. 7, monocytes 3, lymphocytes 40; no abnormal forms. Abortion was induced in early April. The surgical intervention was tolerated well and there was no significant bleeding. Shortly afterwards a rapid exacerbation occurred and all the signs of acute leukemia returned. Renewed treatment was ineffective, and the patient died in June 1950, one year after the onset of the disease. The autopsy findings were those of acute leukemia.

Aminopterin treatment is difficult, especially because the signs of intoxication, notably the aplastic anemia with agranulocytosis and hemorrhagic diathesis, are remarkably similar to those of acute leukemia It now appears to be possible, however, to neutralize even severe signs of intoxication by administration of the aforementioned citrovorum factor.

Available space does not permit of my going into details, such as the dosage, etc., of the treatment. I merely want to emphasize that it is frequently only possible to produce one remission, although cases with several remissions have been reported (17). As has recently been shown in animal experiments, the leukemic cells may apparently become resistant to aminopterin (14, 15).

The PGA antagonists have been tested in the treatment of other neoplasms. Clinical improvement has been shown in a few cases of lymphosarcoma, reticulo-endotheliosis and Hodgkin's disease, but the effect seems to be much less pronounced than in acute leukemia, and no consistent and beneficial effect has been reported in other forms of neoplastic disease.

In conclusion I want to add a few general remarks on the indications for chemotherapy in cancer. A chemotherapeutic agent is either given parenterally or absorbed from the gastro-intestinal tract. If an ideal chemotherapeutic agent were available, this form of administration would obviously offer the immense advantage that all malignant cells in the organism could be reached. But as mentioned in the introduction, sufficiently high concentrations cannot be used without causing damage to normal tissues.

It is therefore evident that the chemotherapeutic agents known at the present time do not offer any advantages in the case of localized tumors, which must either be removed surgically or be effectively dealt with by radiation therapy. It should be borne in mind that radiation has the advantage over chemotherapy that it can be restricted to a certain region. Intra-arterial injections of nitrogen mustards have been tried in order to obtain a higher concentration in circumscribed tumor regions (5, 35), but so far nothing much of practical value seems to have been attained by this method.

Accordingly, chemotherapy is only indicated in generalized diseases, notably generalized hyperplastic disorders of the hematopoietic tissues, such as Hodgkin's disease, leukemias, myelomatosis, reticulolymphosarcomatosis, etc. Chemotherapy should hardly ever be used in localized neoplastic diseases, with the exception of those cases in which a localized active focus cannot be found. This may sometimes be the case in patients with Hodgkin's disease who may be severely intoxicated from a hidden focus. In such cases the nitrogen mustards may be of very great value.

As is known, nitrogen mustards are also used in benign affections, *e. g.* in polycythemia, and may in such cases also have a marked temporary effect. But bearing in mind the carcinogenicity of the nitrogen mustards, we may have good reason, not yet knowing their late effects in human beings, to be hesitant with regard to their use in such affections.

On the whole, the chemotherapy of cancer still presents a large number of unsolved problems many more of which it might be tempting to consider than has been possible in this brief survey, which by no means professes to be complete. Substances other than those discussed might have been included, *e. g.* various bacterial toxins, certain carcinogenic hydrocarbons and radioactive isotopes, the use of which may also, with some propriety, be termed chemotherapy.

It may appear that the prospects of arriving at effective chemotherapy in cancer are rather hopeless, and I fear that the survey is marked by this feeling. Yet I find that although the substances used have a rather unspecific cytotoxic effect, the fact that this effect is not absolutely alike in the various diseases represents a break in the horizon. To give an example, nitrogen mustards are particularly effective in Hodgkin's disease but less active in chronic leukemia, while the reverse holds true of urethane, and the PGA antagonists have their special field of action in acute leukemias and are of but poor value, for example, in Hodgkin's disease. In my opinion, the possibilities cannot be rejected that new substances with an even more selective effect may be developed, or that better results may be obtained by a form of combination therapy.

Finally, there is every reason to call attention to the fact that shortly before the discovery of the sulfa drugs well-known scientists alleged that it would never be possible to develop an effective chemotherapeutic agent against bacterial infections.

SUMMARY

A survey of the action of the antineoplastic chemicals directly affecting cancer cells is given. An illustrative case successfully treated by aminopterin is described. Many of the problems which arise are discussed and the opinion expressed that in the future more selective chemotherapy may be evolved.

ZUSAMMENFASSUNG

Es wird ein Überblick über die Wirkungsweise der antineoplastischen chemischen Stoffe in ihrer direkten Wirkung auf die Krebszellen gegeben. Beschrieben wird ein Fall, der die mit Aminopterin erfolgreich durchgeführte Behandlung veranschaulicht. Es werden viele der sich damit ergebenden Probleme besprochen und es wird der Hoffnung Ausdruck gegeben, dass sich in der Zukunft eine sorgfältiger ausgewählte Chemotherapie entwickeln möge.

RÉSUMÉ

Exposé sur l'action des produits chimiques antinéoplasiques en contact direct avec la cellule cancéreuse. Un cas qui illustre ces faits a été traité avec succès par l'aminoptérine. La plupart des problèmes soulevés sont discutés et l'auteur pense que dans l'avenir une thérapeutique chimique plus sélective pourrait être mise en service.

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FROM THE CLINICAL DEPARTMENT AND THE RESEARCH LABORATORIES, THE RADIUM CENTER FOR JUTLAND (DIRECTOR: PROFESSOR CARL KREBS), UNIVERSITY OF AARHUS, DENMARK.

ACTION OF SOME ANTINEOPLASTIC CHEMOTHERAPEUTICAL AGENTS ON CELL DIVISION[1]

by

Poul Bastrup-Madsen

Some of the compounds which are used in the chemotherapy of neoplastic diseases are cytotoxic substances or cell poisons, which in low concentrations pre-eminently damage the cells by disturbing the mechanism of cell division. If suitably small doses are used, the introduction of such a substance into the organism will result in massive destruction of cells in the tissues in which division is most intense. In the normal organism this applies to cell division in the blood-forming tissues and the intestinal epithelium. Owing to the very active formation of new cells in tumor tissue, the cells of such tissue will be considerably more susceptible to the action of these substances than those of normal tissue. It is difficult to decide how large a part of the therapeutical effect of the substances is due to their mitotic-inhibiting action, but in some of them this action is so conspicuous that it seems reasonable to assume that it is at least of some importance for their therapeutical effect.

The action of the compounds on living cells may, for example, be studied by injecting the agent in question into an animal and then, at regular intervals, removing tissue specimens for histological examination. Another method consists in instilling the agent to be investigated into one eye of an animal, while the fellow eye is used as a control. After the lapse of some time the mitoses in the corneal epithelium are examined. A third and very instructive method by which the action of chemotherapeuticals on living cells may be studied is to add the substances to cul-

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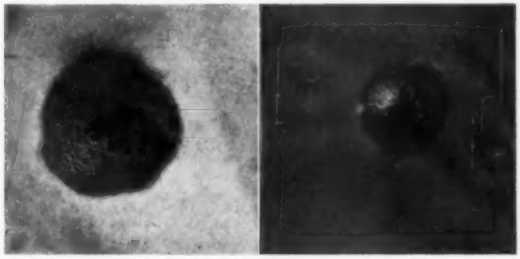

Fig. 1. *Colchicine mitoses.* Cell division is arrested in early metaphase.

tures in which small fragments of tissue are grown in a nutrient medium consisting of plasma and embryonic extract, *e. g.*, from chicks. When various substances are added to the tissue cultures, their effect on the living cells may be observed directly, either by taking a photomicrograph of the living cultures or by microscopic examination of cultures which have been fixed after the lapse of predetermined periods and stained by special methods, depending on the sort of information desired. During recent years, the tissue-culture method has been used to an increasing extent in investigations on the effects of chemotherapeutical agents. By this method the direct action of the substances can be studied, while the possibility exists that in the organism they may undergo a certain transformation. Used in this way, *in vitro* experiments may be a valuable supplement to *in vivo* investigations, since it is possible to form an idea as to whether it is the substance given for therapeutical purposes or a converted product which is active.

The cytotoxic compounds may be divided into three main groups, viz. (1) specific mitotic poisons (spindle poisons), (2) agents with an unspecific cytotoxic effect, and (3) agents with a radiomimetic effect. In the following survey I shall consider the effect of the various forms of cytotoxic substances and discuss certain aspects of the effect of some substances which I have investigated in tissue cultures.

The specific mitotic poisons (spindle poisons) prevent the formation of the spindle. In this way the chromosomes are prevented from moving towards the equator of the cell, so that mitosis is arrested at an early stage of metaphase. *Colchicine* is a typical spindle poison. *Figure 1* shows typical colchicine mitoses, arrested at early metaphase. The chromosomes gradually become pyknotic and the cell disintegrates.

The second group, *agents with an unspecific cytotoxic effect*, consists of a number of different compounds which must be supposed to differ considerably in their mechanism of action. Although their mechanism

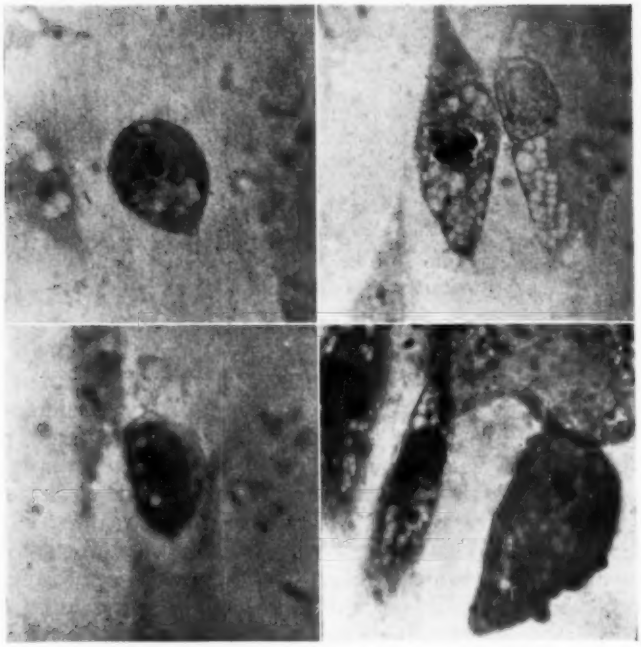

Fig. 2. *Urethane mitoses.* Metaphase arrest; equatorial plates with aberrating chromosomes.

of action has not yet been fully elucidated, these substances must be presumed to interfere with many of the physical and chemical processes which are of importance in the progress of the mitotic cycle. Arsenicals and urethane are examples of compounds belonging to this group. Morphologically, the effects of these are alike, principally manifesting themselves by pyknotic changes in the chromosomes.

Figure 2 shows various chromosome abnormalities induced by *urethane.* Three of the cells have pyknotic equatorial plates with aberrant chromosomes and in the fourth the pyknotic chromosomes are scattered in the cytoplasm. Almost invariably, these chromosome injuries occur at metaphase. Even though these substances — like colchicine — bring about an arrest at metaphase, their mechanism of action seems to be quite different from that of colchicine, since neither urethane nor arsenicals prevent the formation of the spindle.

The diagram (*fig. 3*) shows the effect of urethane, as assessed by differential counts of the various phases of mitosis. The counts are from

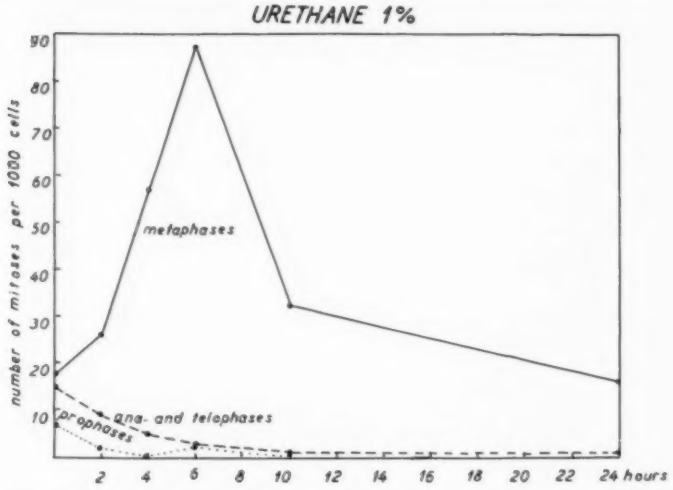

Fig. 3. *The effect of urethane on cell division*, assessed by differential counts of the various mitotic phases. The number of cells at each phase per 1,000 fibroblasts at various times after the administration of a urethane solution (1 %).

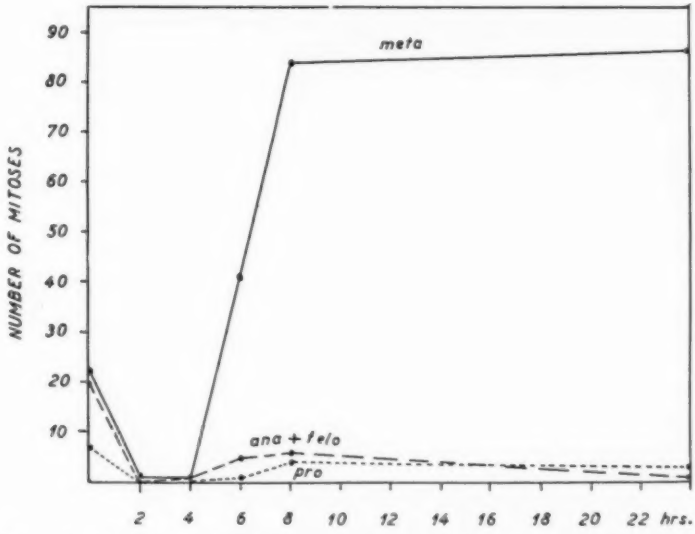

Fig. 4. *The effect of potassium arsenite on cell division*, assessed by differential counts of the various mitotic phases. The number of cells at each phase per 1,000 fibroblasts at various times after the administration of a potassium arsenite solution (0.0005 ‰).

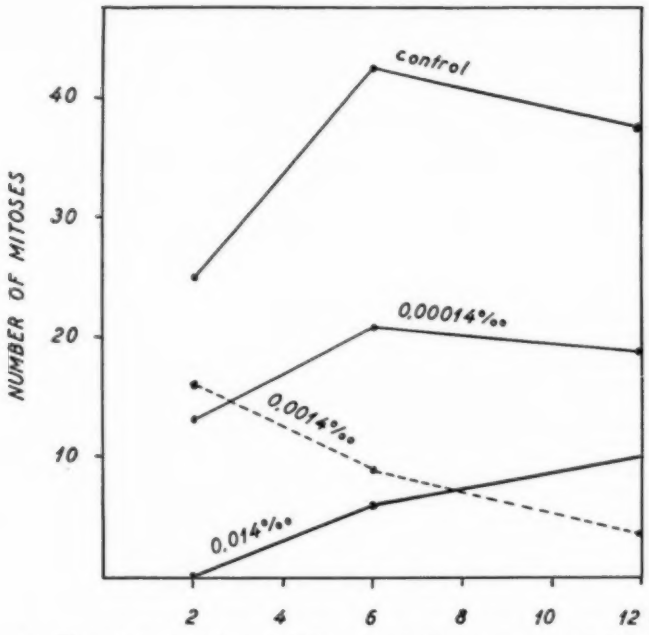

Fig. 5. *The effect of different HN_2 concentrations on the mitotic activity.* The total number of mitoses per 1,000 fibroblasts at various times after the administration of HN_2.

fibroblast cultures to which a urethane solution had been added. It is seen from the diagram that the number of metaphases gradually increased during the first period after the addition. This must be due to an accumulation of arrested metaphases in the cultures, which in turn resulted in a decrease in cells at ana- and telophase, and towards the end there were no cells in these phases. — Further, the number of prophases decreased, signifying that urethane is also capable of reducing the number of cells entering mitosis. The diminished mitotic activity also explains the fall in metaphases later in the experiment.

The next curve (*fig. 4*) similarly illustrates the effect of *potassium arsenite* (Fowler's solution). It appears from the curve that during the first time after the addition no mitoses were observed in the cultures, *i. e.*, the immediate effect of the arsenite was preventing the cells from entering mitosis. Subsequently, cell division was resumed, and just as in the case of urethane, an arrest at metaphase was now observed, resulting in a marked accumulation of cells at metaphase and a simultaneous decrease in the number of ana- and telophases.

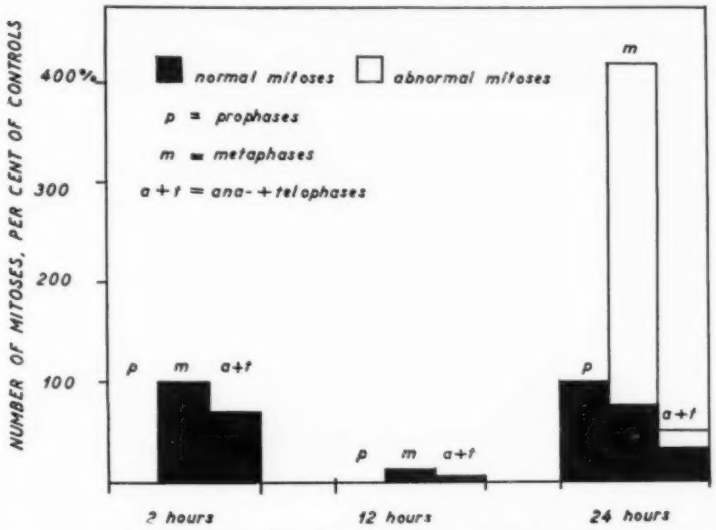

Fig. 6. *The mitoklastic effect 24 hours after the administration of* HN_2. The distribution of normal and abnormal mitoses at an HN_2 concentration of 0.0011 ‰ and the number of cells at each mitotic phase, in per cent of the figures from the controls, at various times after the administration of HN_2.

The *nitrogen mustards* belong to the group of *agents with a radiomimetic effect*. While substances like colchicine, urethane, and arsenite chiefly exert their injurious action on *dividing cells*, the nitrogen mustards affect cells *in the resting phase*. However, the effect cannot be observed until the cells divide after having been exposed to the injurious agent. Here I shall briefly mention the morphological changes induced in the cells by nitrogen mustards.

Temporary Effect. Nitrogen mustards cause a temporary reduction of mitotic activity. *Figure 5* shows the effect of different HN_2 concentrations on the number of mitoses in fibroblast cultures. It will be seen that the number of mitoses was reduced during the first 12 hours after the administration of HN_2. The number of mitoses decreased with increasing HN_2 concentrations.

The next diagram (*fig. 6*) shows the number of the various phases of mitosis at different times after the administration of HN_2. At 2 hours no prophases were present in the cultures, which must mean that no cells, or at least very few, entered mitosis at that time. The number of metaphases was normal. Taking all the phases together, it will be seen that the total number of mitoses was considerably lower than normal.

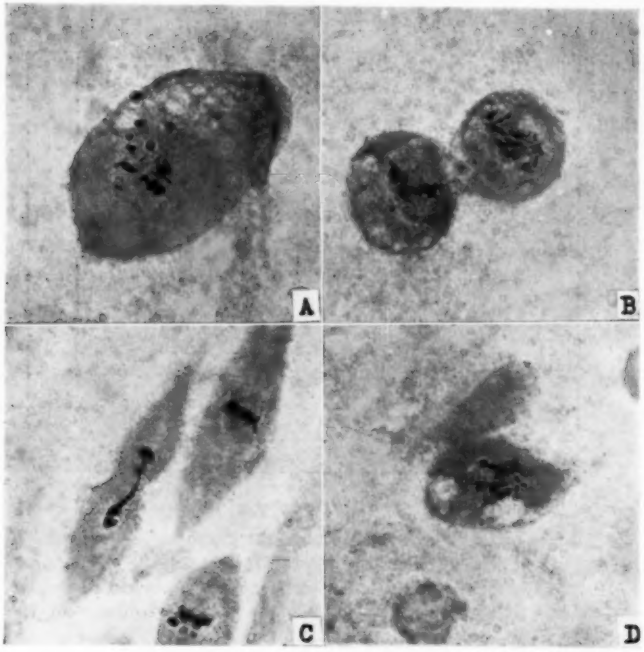

Fig. 7. *Mitotic abnormalities 24 hours after the administration of a nitrogen mustard* (HN_2). A & D: mitoses in metaphase with fragmented chromosomes. B: multipolar mitoses. C: bridge formation in telophase (»stickiness» of the chromosomes).

At 12 hours very few mitoses were observed in the cultures. The black columns represent the number of morphologically normal mitoses, the white columns that of the morphologically abnormal mitoses. The mitoses observed during the first 12 hours were all morphologically normal. At 24 hours the number of prophases present in the experimental cultures was almost identical with that of the controls. This means that the mitotic activity had now been resumed, and that it was of the same intensity as that of the controls. The prophases were morphologically normal. The total number of mitoses was considerably higher than normal. The explanation may be that the progress of mitosis slowed down or was possibly completely arrested in the subsequent phases. It seemed to be mainly at metaphase that this arrest occurred. The majority of mitoses at metaphase and some at ana- and telophase were morphologically abnormal. — I shall later describe the abnormalities observed.

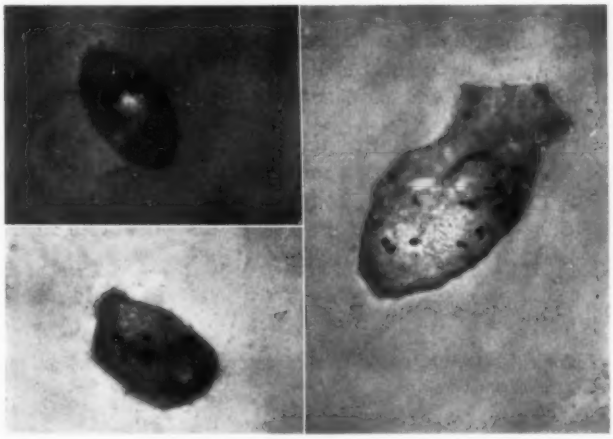

Fig. 8. *Cells degenerating in metaphase 24 hours after the administration of* HN_2.

Permanent Effect. It is characteristic of substances with radiomimetic effect that they do not injure cells which are dividing at the time of their administration. This seems to be in contrast to what has been observed in other mitotic-inhibiting compounds, such as colchicine, urethane, and arsenicals. The radiomimetic effect is exerted on the resting cell, but in such a way that it principally causes damage to such cellular components (chromatic and achromatic) as are related to mitosis. For this reason the injurious effect on the cells will not become apparent until after the lapse of some time, when the cells divide.

The permanent effect of the nitrogen mustards consists in (1) gene mutations, (2) changes in the chromosomal structure, and (3) polarization disturbances.

In this connection, I shall not embark upon the mutagenetic properties of the compounds. The production of lethal genes in the daughter cells may possibly be of some importance for the antineoplastic effect, but no evidence in support of this hypothesis is available.

The therapeutical effect of the substances must surely to a great extent be supposed to be related to their power of producing chromosomal damage and polarization disturbances. The changes which may be encountered are seen in *figure 7*, which shows cells with *chromosome fragmentation* (A, D), a cell with a tendency to *stickiness of the chromosomes* resulting in a bridge formation between the chromosomes at telophase (C), and *a delay in the movements of the chromosomes* (D), by which some of them are left behind at the equatorial plate, while others pass on towards

the poles. Two cells with tripolar mitoses are seen at b. Some of the cells with these abnormalities disintegrated during mitosis (fig. 8), while others seemed to complete the mitotic cycle. However, the daughter cells contained defective chromosome sets and were therefore less viable.

At present our knowledge of the biochemical and biophysical characteristics of the various known inhibitors of mitosis is quite insufficient for an analysis of their actions. It is possible that a useful guide to the mode of action of these substances will be obtained in future from cytochemical studies.

SUMMARY

The morphological effect of colchicine, arsenicals, urethane and nitrogen mustards on dividing cells is described.

ZUSAMMENFASSUNG

Der morphologische Effekt von Colchicin, Arsenikverbindungen, Urethan und Senf-Stickstoff auf die Zellteilung wird beschrieben.

RÉSUMÉ

Description de l'effet morphologique de la colchicine, des arséniates, des uréthanes et des sinapismes nitriques sur des cellules en division.

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FROM THE CLINICAL DEPARTMENT AND THE RESEARCH LABORATORIES, THE RADIUM CENTRE FOR JUTLAND (DIRECTOR: PROFESSOR CARL KREBS), UNIVERSITY OF AARHUS, DENMARK

NITROGEN MUSTARD THERAPY IN HODGKIN'S DISEASE, LYMPHO-RETICULOSARCOMATOSIS AND LYMPHATIC LEUKAEMIA[1]

by

Jørgen Kieler

Since their introduction into clinical medicine by GILMAN and his associates (5) in 1942, nitrogen mustards have been tested in a variety of malignant diseases, notably those involving the hematopoietic system (1, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13).

While Gilman and his group originally used the so-called tris form, tris(beta-chloroethyl)amine hydrochloride, the bis form, methyl-bis (beta-chloroethyl)amine (HN2) has later been preferred because its injection is less commonly followed by local thrombosis (1, 3, 9).

According to the reports so far available, HN2 seems especially to be indicated in generalized diseases, in which surgical intervention is impossible and roentgen therapy less suitable (3, 9, 10, 12). Remissions have been obtained in numerous cases; yet they have generally been of short duration. The agent does not possess any curative effect, but considerable palliation has often been obtained, which must be taken into account in the final establishment of the indications for HN2 therapy. An investigation on the influence of this therapy on the course of the individual symptoms may therefore be of interest.

Case Material

Nitrogen mustard therapy has been used at the Radium Centre in Aarhus since 1947. In most cases, HN2 has been combined with some

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other form of antineoplastic therapy. This report is based exclusively on such cases in which nitrogen mustard has been used as the only antineoplastic agent in some phase of the disease in question, and only cases in which the diagnosis has been histologically verified have been included.

Thirty-six cases, divided into three groups, have been studied:

Group 1 comprises 22 cases of Hodgkin's disease, 7 women and 15 men, whose ages ranged from 20 to 56 years. The duration of disease at the institution of HN2 therapy ranged from 2 months to 6 years.

Group 2 comprises 3 women and 7 men, whose ages ranged from 46 to 76 years, viz., 6 cases of lymphosarcomatosis; 2 cases of reticulosarcomatosis; and 2 cases of lympho-reticulosarcomatosis. The duration of disease varied from 1 month to 7 years.

Group 3 comprises 4 men, aged from 36 to 63 years, with chronic lymphatic leukaemia of a duration from 2 months to 14 years.

Treatment

The standard dosage adopted was 0.1 mg of HN2 (Erasol-Ido) per kg body weight for 7 days, after a test dose of 2 mg. Immediately before use, the preparation was dissolved in 10 ml of physiological saline. If serious dyspeptic discomforts developed, the dose was reduced, and in many cases the treatment was interrupted for a few days.

Prior to each HN2 injection 25 mg of pyridoxine hydrochloride (Benadon-Roche) was given intramuscularly, which in many cases considerably reduced the dyspeptic discomfort.

Blood transfusions were given in 7 cases.

Side Reactions

Nausea and vomiting usually developed during the HN2 therapy. Only in 4 cases there were no dyspeptic discomforts. In 6 cases the untoward effects were considerable, but nevertheless the treatment was completed. In the remaining cases only moderate side reactions were present. Diarrhea was not observed in any case in this series. A decrease of appetite during the course of treatment occurred in all cases. Shortly after the conclusion of the treatment, generally within 5—10 days, the appetite in many cases markedly increased sometimes approaching that of bulimia.

Clinical Results

A total evaluation of the effect shows that in 25 cases an improvement was obtained, by which is understood a distinct diminution of one or more signs or symptoms without signs of simultaneous progression.

The improvement lasted less than 2 months in 15 cases, varied between 2 and 6 months in 5 cases, and exceeded 6 months in 5 cases.

In 11 cases no beneficial effect of the therapy was observed. In 4 of these cases the condition remained unchanged. The remaining 7 patients died during or shortly after the treatment; two of them from complications (arterial bleeding and glottic edema, respectively).

General condition. Symptoms of general debility were stated by 29 patients. Their complaints were: fatigue (25 cases), anorexia (7 cases), definite weight loss (5 cases). Five patients were unable to work.

Following the HN2 treatment a total of 19 patients showed improvement, in 7 cases of more than 2 months' duration; 4 remained unchanged, and in 6 the condition was aggravated.

Itching. Before the institution of HN2 therapy, 17 patients complained of constant itching. In 2 cases this complaint remained unaffected by the therapy, while a considerable improvement was noticed in the remaining 15 cases. Skin changes due to scratching disappeared or abated considerably simultaneously with the subsidence of the pruritus. In 7 cases the improvement lasted more than 2 months, in 4 even more than 6 months.

Pulmonary symptoms. Seventeen patients had pulmonary symptoms. The most common complaint, present in 15, was dyspnea. Ten patients complained of cough; in 5 cases the cough was accompanied by mucopurulent expectoration. In 3 cases the symptoms increased in severity during treatment, and 5 patients remained unchanged. In the remaining 9 patients, the duration of the improvement was less than 2 months in three and more in six; in four of the latter the improvement lasted even more than 6 months.

Dyspepsia. Complaints of dyspepsia before the HN2 treatment were recorded in 8 cases. Four patients complained of vomiting, three of difficulty in swallowing, and two of cardialgia, which in one case was aggravated on ingestion of food, while the other patient developed epigastric pain only on taking alcoholic drinks. One patient stated that his difficulty in swallowing increased after the HN2 therapy. In 4 patients the dyspeptic complaints persisted unchanged after treatment. In the remaining 3 cases a distinct improvement occurred, but lasted less than 2 months.

Pain. A total of 19 patients complained of pain. Back pain, present in 7, was the most common form. Six had pain situated in the extremities; three had abdominal pain, which did not bear the character of cardialgia; two had oppressive retrosternal pain, and two had a painful sensation of oppression on the neck. In 3 cases bone destruction was

other form of antineoplastic therapy. This report is based exclusively on such cases in which nitrogen mustard has been used as the only antineoplastic agent in some phase of the disease in question, and only cases in which the diagnosis has been histologically verified have been included.

Thirty-six cases, divided into three groups, have been studied:

Group 1 comprises 22 cases of Hodgkin's disease, 7 women and 15 men, whose ages ranged from 20 to 56 years. The duration of disease at the institution of HN2 therapy ranged from 2 months to 6 years.

Group 2 comprises 3 women and 7 men, whose ages ranged from 46 to 76 years, viz., 6 cases of lymphosarcomatosis; 2 cases of reticulosarcomatosis; and 2 cases of lympho-reticulosarcomatosis. The duration of disease varied from 1 month to 7 years.

Group 3 comprises 4 men, aged from 36 to 63 years, with chronic lymphatic leukaemia of a duration from 2 months to 14 years.

Treatment

The standard dosage adopted was 0.1 mg of HN2 (Erasol-Ido) per kg body weight for 7 days, after a test dose of 2 mg. Immediately before use, the preparation was dissolved in 10 ml of physiological saline. If serious dyspeptic discomforts developed, the dose was reduced, and in many cases the treatment was interrupted for a few days.

Prior to each HN2 injection 25 mg of pyridoxine hydrochloride (Benadon-Roche) was given intramuscularly, which in many cases considerably reduced the dyspeptic discomfort.

Blood transfusions were given in 7 cases.

Side Reactions

Nausea and vomiting usually developed during the HN2 therapy. Only in 4 cases there were no dyspeptic discomforts. In 6 cases the untoward effects were considerable, but nevertheless the treatment was completed. In the remaining cases only moderate side reactions were present. Diarrhea was not observed in any case in this series. A decrease of appetite during the course of treatment occurred in all cases. Shortly after the conclusion of the treatment, generally within 5—10 days, the appetite in many cases markedly increased sometimes approaching that of bulimia.

Clinical Results

A total evaluation of the effect shows that in 25 cases an improvement was obtained, by which is understood a distinct diminution of one or more signs or symptoms without signs of simultaneous progression.

The improvement lasted less than 2 months in 15 cases, varied between 2 and 6 months in 5 cases, and exceeded 6 months in 5 cases.

In 11 cases no beneficial effect of the therapy was observed. In 4 of these cases the condition remained unchanged. The remaining 7 patients died during or shortly after the treatment; two of them from complications (arterial bleeding and glottic edema, respectively).

General condition. Symptoms of general debility were stated by 29 patients. Their complaints were: fatigue (25 cases), anorexia (7 cases), definite weight loss (5 cases). Five patients were unable to work.

Following the HN2 treatment a total of 19 patients showed improvement, in 7 cases of more than 2 months' duration; 4 remained unchanged, and in 6 the condition was aggravated.

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Pulmonary symptoms. Seventeen patients had pulmonary symptoms. The most common complaint, present in 15, was dyspnea. Ten patients complained of cough; in 5 cases the cough was accompanied by mucopurulent expectoration. In 3 cases the symptoms increased in severity during treatment, and 5 patients remained unchanged. In the remaining 9 patients, the duration of the improvement was less than 2 months in three and more in six; in four of the latter the improvement lasted even more than 6 months.

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demonstrated. In 5 cases of Hodgkin's disease, unchanged or increasing pain was present after treatment. Fourteen patients showed improvement, lasting less than 2 months in 10 cases, and more than 5 months in 4 cases.

Enlargement of lymph nodes. Enlargement of superficial nodes was found in 33 cases. In 18 patients, two of them with rapid growth of the superficial lymph nodes, the HN2 therapy did not produce any demonstrable improvement. In the remaining 15 patients, who showed improvement, the effect lasted less than 2 months in 8 cases, and more than 4 months in 7 cases.

Mediastinal tumor. In 18 cases an increase of width of the mediastinal shadow and/or enlarged hilar lymph nodes were observed. In three of these patients the condition was aggravated by the treatment, while in five it remained unchanged. Improvement was seen in 10 cases, but only in three of them did it last more than 2 months.

Osseous changes. Bone destruction was demonstrated in 3 patients. Two of these cases did not improve during treatment. In 1 patient with lymphosarcomatosis a tumor, the size of a clenched fist, was seen above the sternum; it disappeared completely during treatment. A roentgenogram revealed a large defect in the sternum. Partial healing occurred after treatment and the improvement lasted 10 months.

Skin lesions. Three patients had skin changes due to causes other than scratching. In 1 patient with Hodgkin's disease signs of erythroderma disappeared, now without recurrence for more than 2 years. Of two patients with reticulosarcomatosis and cutaneous infiltrations, one improved for 3 months, while the other remained unchanged.

Lesions of various organs. Signs of involvement of various organs were disclosed in 19 cases. Pulmonary infiltration was found in 8 cases, enlargement of the liver in 8, swelling of the spleen in 5, signs of intestinal infiltration in 1, and infiltration of the corpus mammae in 1 case. In addition, signs of nephrosis were found in 1 case, atelectasis in 1, pleural effusion in 3, pericarditis in 1, and ascites in 1 case. Eight patients did not improve after treatment. In 11 the signs subsided considerably, but only in 3 cases did the improvement last more than 2 months. A distinct enlargement of the liver disappeared in 5 cases after HN2 therapy. In 3 patients a definite subsidence of the pulmonary changes was seen, and in 2 cases the enlarged spleen decreased in size. A considerable reduction in the size of a large tumour of the thyroid gland occurred in one patient and in another a large abdominal tumour subsided. Freedom from signs was obtained in 1 case of mammary infiltration and in 1 case of intestinal infiltration. One case of a large pleural effusion and 1 case of an extensive atelectasis almost cleared up during treatment.

Fever. At the institution of HN2 therapy 18 patients had fever. In 16 patients the temperature returned to normal, mostly in 3—5 days, in a few cases after 8—10 days. Only 3 patients, all with Hodgkin's disease, remained afebrile for more than 2 months.

Thus, an effect partly on the local processes and partly more general has been obtained.

The regression of local processes has resulted in an improvement of focal symptoms, such as pulmonary complaints, focal edema, dyspeptic discomfort, and pain.

However, the general effect has been much more conspicuous, evidenced by increasing strength, improved appetite, subsidence of itching, fall of temperature and to some degree by disappearance of non-focal pain.

The effect varied somewhat within the three groups. Only 1 of the 4 leukaemic patients showed essential improvement. In the two other groups the relative number of cases of immediate improvement was roughly alike, although the patients of these two groups responded to treatment in different ways. Thus, in the group of lympho-reticulosarcomatosis a far more pronounced effect was noted on focal complaints, such as pulmonary symptoms, pain, enlargement of superficial and mediastinal lymph nodes, and lesions of various organs.

When, nevertheless, the final evaluation does not give any definite difference between the two groups, this is due to the favorable effect of the HN2 therapy on the generalized symptoms, notably fever and itching, which are far more dominant in Hodgkin's disease than in lympho-reticulosarcomatosis.

In addition, the difference in the immediate effect does not reflect a corresponding difference in the influence of the therapy on the subsequent course of the disease. On the contrary, after two months signs of renewed progression were present in three fourths of the improved patients with lympho-reticulosarcomatosis, while relapse occurred in only slightly more than one half of the improved patients with Hodgkin's disease.

Immediate effect on the blood. Blood examinations were done twice a week during the treatment. One patient with lymphosarcomatosis died before the first blood control.

The erythrocyte count increased during treatment in 6 cases. The increases occurred gradually and were in no case due to blood transfusion. In 16 cases only insignificant variations were seen, although a tendency to slight falls was generally present. A distinct fall in the count occurred in 13 cases.

The leukocyte count increased during treatment in 2 cases, remained unchanged in 6 cases, and decreased in 23 cases. In 5 of the latter cases leukopenia developed. Changes in the number of immature cell forms were not encountered.

The thrombocyte count increased during treatment in 6 cases, while it remained fairly unchanged in 12 cases. In 17 patients a drop was seen, in 14 of them to less than 200,000.

The sedimentation rate increased during treatment in 2 cases, remained unchanged in 19, and decreased in 14 cases.

Thus, there was a markedly depressive effect on the hematopoiesis. However, actual cases of agranulocytosis and thrombopenic hemorrhage did not occur. Blood transfusions proved effective in all cases of penia induced by the HN2 treatment.

HN2 therapy was not considered contra-indicated in the presence of low initial values, if anything, rather the opposite. In several cases the desired effect was also obtained. Thus, a considerable increase in the erythrocyte count occurred in 5 out of 11 cases with initial values below 3,000,000, while a drop was observed only in 2 cases within the same group. Correspondingly, an increase in the thrombocyte count was encountered in 5 out of 10 cases with initial values below 200,000, while a drop occurred only in 2 cases. Of 2 cases with initial leukopenia, the leukocyte count increased in one and decreased in the other.

Renewed Course of HN2

Renewed HN2 therapy was attempted in 8 cases. Four injections of 0.1 mg per kg body weight were given. In 1 patient the first course did not produce any improvement. After subsequent roentgen therapy the condition of the patient was aggravated and another course of HN2 was attempted, also without success. The patient died shortly afterwards. All the remaining 7 patients had shown improvement after the first course of HN2. By renewed therapy good effect was obtained in 3 patients for about 3 months. Four patients died shortly after the second course of HN2.

Conclusion

On the introduction of new therapeutic agents in the treatment of neoplastic diseases the assessment of their clinical value must to a great extent be made on the basis of a comparison with the results which may be obtained by roentgen therapy. Such comparisons have limited the field in which nitrogen mustard may be used to generalized diseases, since far more intensive treatment may be attained in local processes by means of roentgen rays.

In this series subsequent roentgen therapy proved ineffective in 2 cases which did not respond to HN2. Ten patients who improved after HN2 were subsequently treated with roentgen, with improvement in six cases.

Twenty-two patients had previously received roentgen treatment with varying effect. In 9 cases no improvement was noted after the last course of roentgen. In 5 of the latter cases palliation followed after subsequent HN2 therapy. The effect, which was only of short duration, consisted in an improvement of the general condition, diminished itching, fall of temperature, and subsidence of non-focal pain, which was probably to be regarded as a manifestation of the general muscular debility. All these symptoms had been present prior to and remained unaffected by the last course of roentgen before the institution of HN2 therapy. On the other hand, in no case did HN2 produce any greater effect on focal processes than roentgen.

The conclusion of the present investigation must therefore be that pronounced generalized symptoms, notably fever and itching, but also fatigue, anorexia, loss of body weight, and, to some extent, pain, anemia, and thrombopenia constitute special indications for HN2 therapy. On the other hand, according to reports so far available, the greatest beneficial effect on focal signs is obtained by roentgen therapy. In cases of generalized disease unsuited for roentgen treatment a more pronounced improvement of the focal signs may be expected in lympho-reticulosarcomatosis than in Hodgkin's disease. In such cases it would, however, be rational to attempt a combination of HN2 and roentgen rays, the latter being specially directed to large and symptom-producing processes.

Finally, it should be mentioned that HN2 therapy may be specially indicated in Hodgkin's disease without any demonstrable focus (2). In the series there was only one case of this type. A considerable improvement due to the treatment occurred, evidenced by a return to normal temperature, disappearance of abdominal and thoracic pain, and subsidence of subileac attacks. However, in the course of 1 month signs of progression were seen and enlargement of the superficial lymph nodes occurred. The patient died 1 week later.

SUMMARY

The results obtained in 22 cases of Hodgkin's disease, 10 cases of lympho-reticulosarcomatosis, and 4 cases of chronic lymphatic leukaemia treated by HN2 are reported. The indications for its use as well as for roentgen therapy and for a combination of the two in these diseases are discussed in full.

ZUSAMMENFASSUNG

Die Ergebnisse mit HN2 Behandlung von 22 Fällen von Lymphogranulomatose (Hodgkin's Granulom), von 10 Fällen von Lympho-Retikulosarkomatose und von 4 Fällen von chronischer lymphatischer Leukaemie werden berichtet. Die Indikationen für diese Behandlung, für die Röntgenbestrahlung und für die Kombination dieser beiden Therapieformen bei den obengenannten Erkrankungen werden erschöpfend besprochen.

RÉSUMÉ

Les résultats obtenus par l'application de HN2 dans 22 cas de maladie de Hodgkin, 10 cas de sarcomatose lymphoréticulaire et dans 4 cas de leucémie lymphatique chronique sont relatés. Les indications de ce traitement comme celle du traitement radiologique et leur combinaison dans ces maladies sont sérieusement discutées.

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FROM THE RADIUM CENTRE FOR JUTLAND AND THE ROENTGEN DEPARTMENT OF THE MUNICIPAL HOSPITAL, AARHUS, DENMARK (DIRECTOR: PROFESSOR CARL KREBS)

TRIETHYLENE MELAMINE THERAPY IN HODGKIN'S AND OTHER MALIGNANT DISEASES[1]

by

P. Bjerre Hansen and *J. Bichel*

During the past year a new compound, triethylene melamine, has been added to the group of chemicals with an inhibitory effect on tumor growth. Chemically, it belongs to the polyethylenimines and was originally intended for improving the finish of rayon fabrics. Because of their high chemical reactivity with organic molecules, the action of these compounds on tumor growth was studied in the Sloan-Kettering Institute in New York (1, 2, 4, 6). Triethylene melamine (TEM) proved to be extremely active in this respect.

Further detailed investigations showed that the properties of TEM were in many respects similar to those of nitrogen mustards. The two substances are also chemically related, as expressed by the ethylenimonium transformation of the nitrogen mustard molecule. This is seen from the formula of the most commonly used nitrogen mustard, methyl bis-(2-chlorethyl)amine (HN2). — As contrasted with HN2, TEM has only a slight effect on the central and parasympathetic nervous systems. In addition, TEM is water soluble and is active at a considerably lower pH than HN2. These characteristics facilitate intravenous administration and make also oral administration possible.

Following the experimental investigations, TEM was tested clinically in the treatment of various malignant disorders, particularly Hodgkin's disease, chronic leukemias and lymphosarcomas (Memorial Hospital, New York). A preliminary report (7) was published in the summer of 1950, followed by a more detailed report in April 1951 (3). Independent

[1] Read before the 17th Congress of the Northern Association for Medical Radiology, at Aarhus, June 1951; submitted for publication, June 18, 1951.

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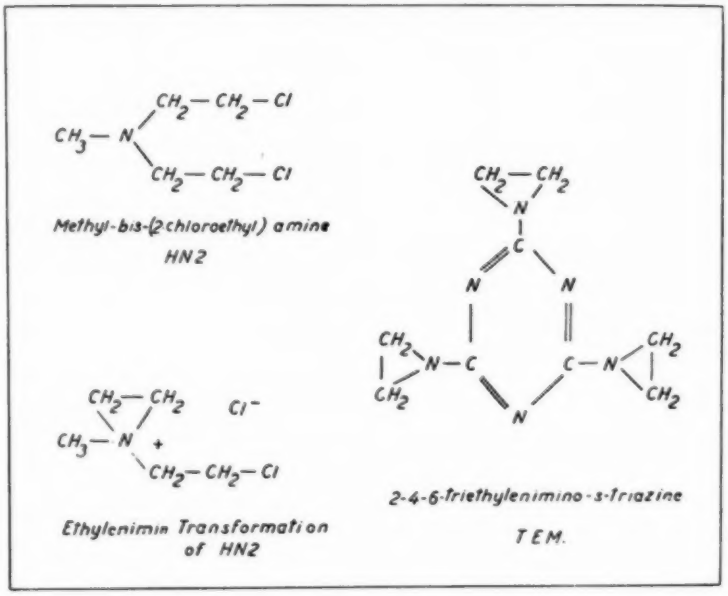

experimental and clinical investigations of TEM (»9500») has been carried out in England (5, 8). Since October 1950 TEM has been used clinically in the Radium Centre for Jutland in the therapy of Hodgkin's and allied malignant diseases.

Case Material

So far (1. 3. 1951) 15 patients have been treated, viz.:

Hodgkin's disease	9 cases	(Nos. 1— 9)
Chronic lymphatic leukemia	2 —	(Nos. 10—11)
Myelomatosis	2 —	(Nos. 12—13)
Reticulosarcomatosis	1 case	(No. 14)
Cancer of the breast with metastases	1 —	(No. 15)

Only patients suffering from generalized or widespread disease have been selected for TEM therapy. This means that the course of disease was chronic or subchronic in the majority of the cases. Accordingly, only three of the patients, all of them with Hodgkin's disease, were previously untreated (Nos. 4, 7 & 9). All the remainder had previously been treated with roentgen rays, nitrogen mustards, stilbamidine etc., some of them many times during several years. Seven female and eight male patients, being from 14 to 71 years old, have been treated.

Administration of TEM and Side Effects

TEM has been administered solely by the oral route, in tablet form[1] in single doses ranging from 1.25 to 5 mg. In most cases a total initial dose of 10—20 mg was given, spread over 8—10 days. After an interval of 2—3 weeks the treatment was in some cases continued with smaller doses of 2.5— 5 mg per week for varying periods of time, either until the desired effect was obtained or as maintenance therapy. — As all organic substances will interfere with the absorption of TEM, it has to be taken on an empty stomach in the morning together with a glass of plain water, and breakfast should be withheld for one hour. — The administration of TEM is sometimes followed by slight nausea, a feeling of oppression and vomiting. These side reactions usually begin 5—6 hours later and may last for the rest of the day. Since the same side reactions occur after intravenous injection (3, 7), it is not a question of any local effect. However, the nausea is not by far so severe or constant as after HN2, and vomiting is infrequent. — These rather harmless side reactions do not play any rôle in the accomplishment of the TEM therapy. Of extreme importance, on the other hand, is the influence of TEM on the blood forming tissues. — Like HN2 and other nitrogen mustards, urethane, etc. as well as radioactive substances and whole-body irradiation, TEM has the properties of a general cell poison and is capable of producing a severe depression of the bone marrow functions. As this effect is very pronounced, the therapeutic range of TEM is extraordinarily narrow. Furthermore, the depression of the hematopoiesis is delayed, the maximum depression usually occurring 2—3 weeks after the beginning of therapy. Consequently, the patients must be followed carefully with close hematological studies not only during the treatment but also for a considerable time after the treatment with TEM.

Results

The effect of the therapy was evaluated according to subjective and objective improvement. The principal signs and symptoms considered were recorded in the following 10 main groups:

Symptoms:

1. General condition	Fatigue, weakness, loss in body weight, etc.
2. Pruritus	Itching, night sweats, etc.
3. Pulmonary symptoms	Cough, dyspnea, expectoration, etc.
4. Dyspeptic symptoms	Cardialgia, nausea, vomiting, etc.
5. Pain	Pains in the back, joints, abdomen, retrosternal pains, etc.

[1] We are indebted to the Lederle Laboratories for supplying the Triethylene Melamine tablets.

Signs:

6. Enlarged lymph nodes ..... All peripheral lymph nodes.
7. Mediastinal tumor ..... Hilar and mediastinal lymph nodes.
8. Affection of various organs or systems of organs ..... Lungs and pleura, gastro-intestinal tract, spleen, abdominal lymph nodes, etc.
9. Bone destruction.
10. Fever.

In addition, the blood counts, the hemoglobin level, and the sedimentation rate were considered, the hematological factors being of special interest in the cases with leukemia. — The condition of the individual patients before the treatment was compared with their condition 3—4 weeks after the discontinuance of the treatment (*i. e.* the immediate result) as well as with their state at monthly follow-up examinations during the next 5—6 months.

It should be emphasized that since TEM therapy is only palliative, the principal aim must be to relieve the patients of as many subjective complaints and symptoms as possible without causing any severer injury. The objective signs as such are of secondary importance.

In the *Hodgkin group*, the immediate palliative effect was decidedly good in 5 and moderate in 2 cases, while TEM therapy proved to be without value in the remaining 2 cases. Improvement comprised in particular relief or disappearance of itching, cough and pains as well as reduction of enlarged peripheral lymph nodes and attainment of normal temperature. The remissions obtained were usually of short duration. Only in two patients, both of them previously untreated, did the improvement extend over 4—5 months (Nos. 7 & 9). In four cases relapses occurred after 2—3 months. One of these patients (No. 3) showed good response to a subsequent course of roentgen treatment. In two others (Nos. 2 & 6) TEM therapy was resumed with good immediate effect. The benefit, although moderate in time, of TEM therapy in these two cases is remarkable, since both the patients had previously received many courses of treatment, both with HN2 and roentgen rays, with gradually diminishing effect. One patient, previously untreated, showed a definite immediate improvement, but during a subsequent attempt to establish a maintenance therapy a fatal aplastic anemia developed. (No. 4.) The two patients without benefit from treatment died of their disease 4 and 7 months later. (Nos. 1 & 8.)

In the *miscellaneous group* one patient with chronic lymphatic leukemia showed an immediate improvement, but shortly afterwards an aplastic anemia developed and the patient died one month later. No response was seen in the remaining five cases. The other patient with leukemia died 2 months later, and the two patients with multiple myelo-

mas died 2—3 months later. The patient with cancer of the breast died 4 months later. They died all of their progressing disease. The last patient, a man with generalized reticulosarcomatosis, received only 5 mg TEM, no therapeutic effect was seen, but the treatment was stopped because of a rapid downfall of the platelet and granulocyte counts. TEM therapy was resumed 4 months later with very small and fractionated doses, 1.25—2.5 mg at intervals of 8—14 days. This maintenance therapy proved successful for more than four months.

A study of the results published by the American investigators (3) shows that a definite improvement lasting more than 3—4 months was obtained with oral TEM therapy in 5 out of 19 patients with generalized or widespread Hodgkin's disease; in 2 of 7 patients with chronic lymphatic leukemia; in 2 of 8 patients with chronic myeloid leukemia; and in 2 of 8 patients with lymphosarcomas. An obvious immediate improvement was, as in our material, a fairly constant feature especially in the Hodgkin group; but the remissions were mostly of only short duration. Similar results has been obtained at the Harlem Hospital (9), New York (14 cases), at the Holt Radium Institute (5), Manchester (16 cases) and at the Royal Cancer Hospital, London (personal communication). As a whole, the American and the British results correspond to each other and to those obtained in our limited case material.

Depressive Effect on Hematopoiesis

Finally, the marked inhibitory effect on the hematopoiesis is to be considered in some detail. Only 4 of the 15 patients treated with TEM showed no appreciable affection of the bone marrow. In 6 of these 11 cases an intense depression developed, particularly of the granulocytopoiesis and the thrombopoiesis. As previously pointed out, this depression of the hematopoiesis developed in case 4 into a fatal aplastic anemia. An aplastic anemia also developed in two other cases, Nos. 11 and 12, but here coincided with a distinct progression of the disease, leukemia and myelomatosis, respectively. Both the patients died. In the remaining 3 cases with severe affection, the hematopoiesis recovered after intense treatment with blood transfusions, B_{12}, folic acids, antibiotics, etc. One of these patients (No. 10) died of the disease, leukemia, about 3 months later; the two others (Nos. 9 & 14) both survive without any hematological changes.

The curves showing the blood counts and hemoglobin level in two of the patients with severe affection of the hematopoiesis (Nos. 4 & 9) distinctly illustrate the violent depressive effect. It is noteworthy that the depression is of insidious and delayed onset and persists for a comparatively long time. It closely corresponds to the effect of whole-

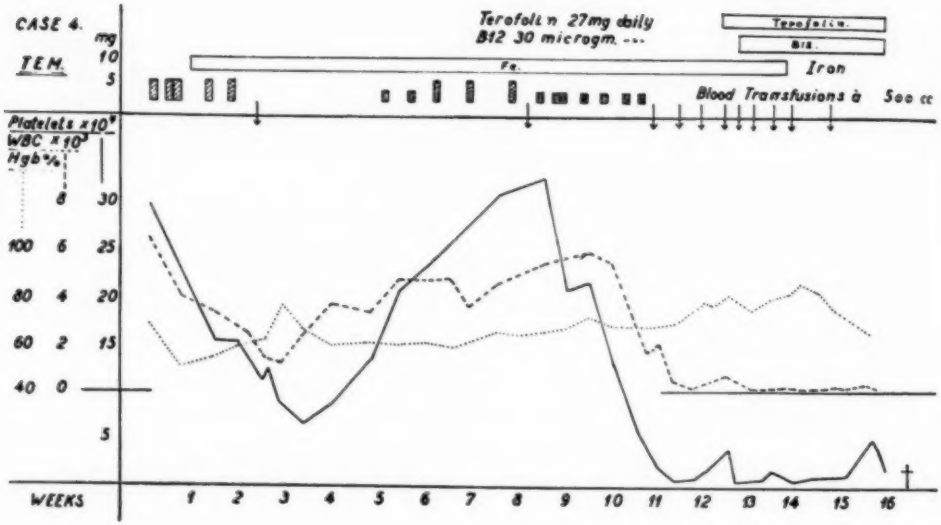

Diagram 1

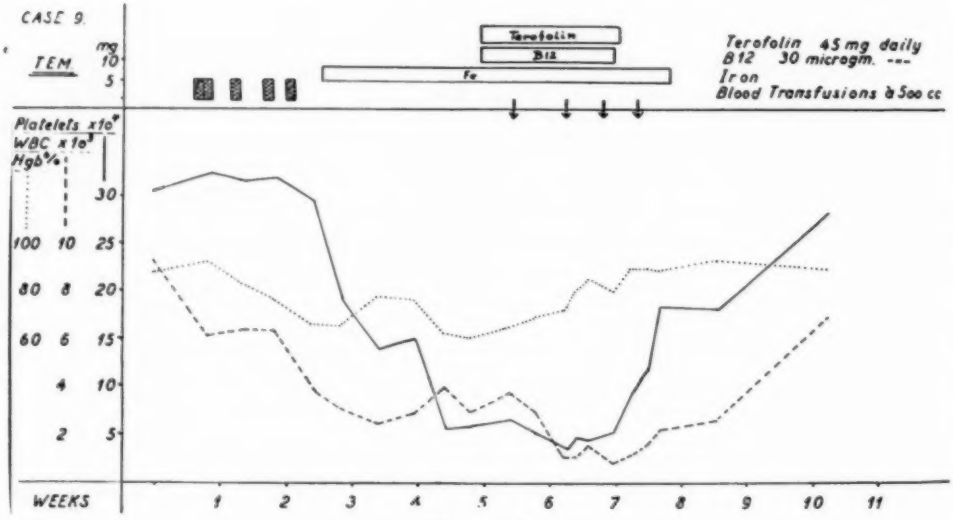

Diagram 2

body roentgen treatment, while the nitrogen mustards rarely produce such an extensive and long-continued arrest of the functions of the bone marrow.

Conclusion

Thus, TEM has a considerable, although transient, palliative effect on a variety of malignant diseases, particularly Hodgkin's disease, chronic leukemias, lymphosarcomas and allied disorders. The inhibitory action on tumor growth is not selective; TEM is a general cell poison and has especially a protracted, highly depressive influence on the hematopoiesis. It has few and moderate acute side reactions and may be administered orally and is thus a convenient drug for clinical use. Through a cautious fractionated administration it seems sometimes to be possible to arrive at a maintenance therapy with small periodic doses of TEM.

SUMMARY

Some clinical experiences with triethylene melamine are reported. The treatment resulted in good immediate improvement in 7 of 9 cases of Hodgkin's disease and in 1 of 2 cases of chronic lymphatic leukemia as well as in 1 case of reticulosarcomatosis. The effect is only palliative and temporary. Remissions exceeding 5—6 months have so far only been observed in 2 cases. In 2 cases of multiple myelomas and in 1 case of cancer of the breast no improvement was seen. The chemical and cytotoxic properties are closely related to those of the nitrogen mustards and in some respects also connected with the effect of whole-body irradiation. The administration of triethylene melamine is easy; it may be given by mouth and has few acute side reactions.

ZUSAMMENFASSUNG

Klinische Erfahrungen mit Triaethylenmelamin werden berichtet. Die Behandlung ergab in 7 von 9 Hodgkinfällen und in 1 von 2 Fällen mit chronischer lymphatischer Leukaemie gute unmittelbare Verbesserung; in einigen wenigen Fällen von multiplen Myelomen, Retikelzellsarkomen und Brustkrebsen wurde keine Besserung beobachtet. Die chemischen und zytotoxischen Wirkungen sind den bei Stickstoff-Lost-Behandlung und in gewisser Beziehung den bei der Totalbestrahlung auftretenden sehr eng verwandt. Die Verabreichung von Triaethylenmelamin ist einfach: es kann per os gegeben werden und hat wenig heftige Nebenwirkungen.

RÉSUMÉ

Quelques expériences cliniques portant sur la mélamine triéthylène sont relatées. Le traitement donna une amélioration immédiate dans 7 cas sur 9 de maladie de Hodgkin, dans 1 cas sur 2 de leucémie lymphatique chronique, comme dans un cas de réticulosarcomatose. L'effet n'est cependant que palliatif et temporaire. Jusqu'ici des rémissions excédant 5 à 6 mois n'ont été observées que dans deux cas. Dans 2 cas de myélomes multiples et dans 1 cas de cancer de la poitrine il n'y eut aucune amélioration. Les propriétés chimiques et cytotoxiques sont minutieusement comparées à celles des sinapismes azotés et, à certains points de vue, à celles de l'irradiation générale du corps. L'administration de la mélamine triéthylène est simple, on la donne par la bouche et elle provoque peu de complications aiguës.

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FROM THE ROYAL NORTHERN HOSPITAL, PHYSICS DEPARTMENT, LONDON, ENGLAND.

BERYLLIUM-WINDOW TUBE OUTPUTS; FURTHER CONSIDERATIONS REGARDING THE USE OF CONSTANT AND PULSATING TENSION[1]

by

W. Alan Jennings

Introduction

In a previous communication (JENNINGS, 1950), comparisons were made between the experimental results obtained by the writer using a beryllium window tube operated under pulsating tension (2—50 K. V. P.) and those obtained by BRAESTRUP (reported by ROGERS, 1947) with constant potential equipment. The latter's measurements were confined to a range of aluminium filtrations at 50 K. V., and a tube current of 2 mA only was used in order to limit dose rates to a maximum of ≈ 3,000 r/min. The chamber employed by BRAESTRUP was a standard free-air chamber from the National Bureau of Standards (TAYLOR, 1951), and not an adaptation of the original one described by TAYLOR and STONEBURNER (1932) combined with a »mesh» design evolved by QUIMBY and FOCHT (1943) — as erroneously implied in the writer's earlier paper on the subject. Thus, Braestrup's measurements may be regarded as the most reliable data for comparison purposes, providing that »output» is confirmed to be proportional to tube current where maximum dose rates are considered (at 50 mA and constant potential). In this connection, the National Bureau of Standards chamber has now been further evolved to measure dose rates up to 10^5 r/min., ionic recombination losses being prevented, at a field strength of 200 volts/cm, by reducing the beam diameter from 8.0 to 0.5 mm (TAYLOR, 1951). However, no detailed air dose rate data thus measured have yet been published.

In the comparison previously reported it was stated that Braestrup's constant potential results (at 50 K. V.) and the writer's pulsating ones

[1] Submitted for publication, March 21, 1951.

(at 50 K. V. P.), expressed in terms of r/min/mA[1], were in a ratio of approximately 8 : 5 over the entire range of filtration, except under zero filtration, where the ratio fell to 8 : 6. It was suggested that this change in the ratio might be due to the presence of a window thickness of 1.2 mm instead of the nominal 1.0 mm beryllium in the tube used by the writer, for the effect of such a difference would only become significant when the external filtration was low or zero.

The additional window thickness was primarily postulated to account for a small beam hardening observed by comparison with some theoretical data. However, it has since been realised that this hardening effect can be attributed to the small penetration of the cathode rays into the target material (set at 22° to the vertical) — an effect of significance for such soft transmitted radiation qualities, and for which no allowance had been made in the corresponding theoretical analysis. Moreover, this latter factor is applicable to both the Units used by BRAESTRUP and the writer, and thus would not account for the change in the output ratio.

It is the purpose of this communication to indicate how the fall in the above output ratio under low filtration was in fact to be expected from K. V. (and tube current) wave-form considerations.

Theoretical Approach

Relative roentgen-ray outputs under constant and pulsating potential generation have now been derived by the writer by means of a theoretical analysis based on the work of KRAMERS (1923). Thus, by applying the latter's formula regarding continuous roentgen-ray spectra, together with the values of the relevant absorption coefficients, to the K. V., filtration, and F. S. D. ranges and materials concerned, full spectral distributions of the radiations emitted under a wide range of K. V.'s and filtrations (beryllium plus aluminium and air) have been derived. From these, planimeter measurements provided relative outputs directly, and by interpolation, for any K. V., filtration, and F. S. D.

To convert this constant potential data to that under the pulsating tension used in the experimental work, a knowledge of the actual K. V.- and tube current wave-forms is required, and these were measured simultaneously with the aid of a double-beam oscillograph, as shown in figure 1. The constant potential data was then applied graphically to the actual wave-forms, and the relative outputs under pulsating tension derived by further planimeter measurements. In this case, »tube current» forms an additional variable to the three listed above.

Working independently BUSH (1950) has also derived some of the

[1] In the writer's pulsating tension equipment, the tube current indication is the average value.

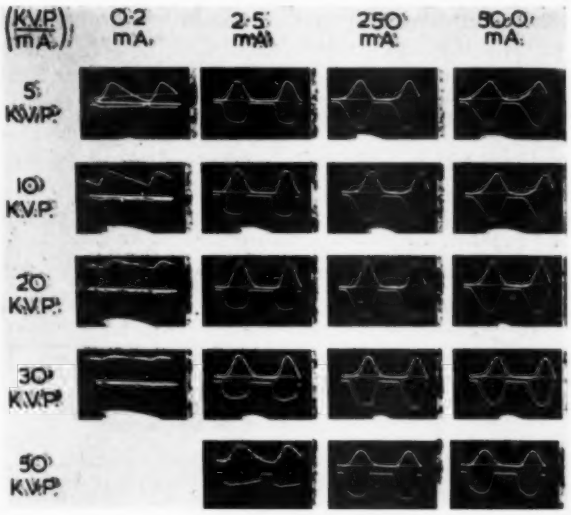

Fig. 1. Measured K. V. and tube-current wave-form pairs. These wave-forms are here individually amplified to produce similar dimensions.

theoretical results referred to above, though without the use of the actual wave-forms involved, and his results were included in the writer's earlier paper. The present more extensive analysis not only enables one to compare theory with experiment, but provides a direct relation between actual outputs and qualities under both types of generation — which is the present concern.

Outputs under Constant and Pulsating Tension

For a given (average) tube current (50 mA), the relative outputs at 50 K. V. P and 50 K. V., at 30 K. V. P. and 30 K. V., etc., are given graphically in terms of ratios in figure 2.

One of these theoretical curves can be compared to published experimental work — namely, the ratios of Braestrup's 50 K. V. data to the writer's at 50 K. V. P. over a range of filtrations at 10 cms F. S. D., and these are given in Table I.

Comparison of the last two columns yields satisfactory agreement, both as regards the fall in the ratio under low filtrations, and in regard to magnitude throughout.

At the suggestion of Dr. F. Bush, a stroboscopic device has recently been developed which provides a means of measuring the actual output

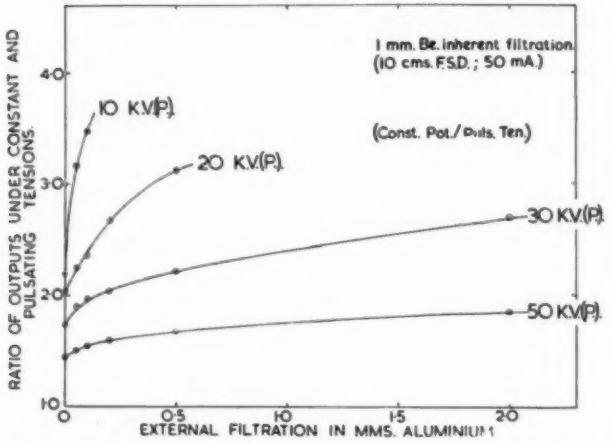

Fig. 2. Theoretical relative outputs under constant and pulsating tension, indicating K. V. (P.) and filtration dependence.

Table I

External filtration in mms. aluminium	Outputs in r/min/(av.) mA		Ratios of outputs: Const. P./Puls. T.	
	Const. P. (C. B. Braestrup; Rogers, 1947)	Puls. T. (W. A. Jennings, 1950)	CBB/WAJ expt.	Theory (Fig. 2)
0.0	1,555	1,180	1.31	1.44
0.05	903	680	1.35	1.49
0.1	605	440	1.37	1.54
0.5	104	64.2	1.62	1.68
2.0	25.7	13.2	1.95	1.86

wave-form. Moreover, by employing the »peak» setting only, approximately constant potential radiations can be »extracted», and their properties compared experimentally with the pulsating tension data. The interpretation of a single measured output wave-form presents certain difficulties (particularly as regards ionic recombination losses at high dose rates), but the relation of peak height to area forms a numerical measure which can be compared with the corresponding ratio for different K. V. P. settings under a chosen filtration. Thence, by using the 50 K. V. (P.) curve as basis, points lying on the three other K. V. (P.) curves have been experimentally derived. Covering a range of 0.1 to 2.0 mm aluminium filtration, these points all fall within 10 % of the theoretical curve values,

but as this stroboscopic work[1] is still in its preliminary stages, and has other applications, a detailed report of the technique will not be given at present.

Some other Theoretical Results

The dependence of three other radiation characteristics on the respective use of constant and pulsating tension have been investigated, and the results are all included in figure 3.

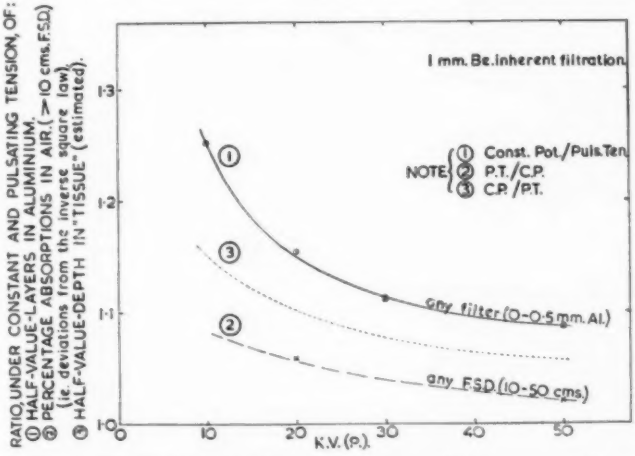

Fig. 3. Theoretical relative radiation qualities, penetrations, and absorptions in air under constant and pulsating tension.

(1) The ratio of *radiation qualities* expressed in terms of half-value-layer (H. V. L.) in aluminium, under the two types of generation (C. P./P. T.), is seen to rise with fall in K. V. (P.), but has been found to be little influenced by changes in external filtration (0.0 to 0.5 mm Al.). One point of comparison is possible — the ratio of Braestrup's H. V. L. data derived at 50 K. V. to that of the writer's at 50 K. V. P. The mean value of this ratio is 1.09, in agreement with the theoretical curve (figure 3, 1), though there is some fluctuation with filtration. However, these fluctuations are random, confirming to some extent the independence of this factor from filtration.

(2) Similar relationships (to those for H. V. L.) are found to hold for the relative *absorption of the beam in air* under the two types of generation. Thus, the ratio (figure 3, 2) of the respective air losses (*i. e.*, P. T./C. P.) is found to rise with fall in K. V. (P.), and to be little influenced by the

[1] Carried out in collaboration with Dr. BUSH.

F. S. D. concerned (10 to 50 cms). This curve can be compared with some experimental work by considering the relative air loss factors published by the writer (Acta radiol. Vol. 33, pp. 456—7) under pulsating tension and those published by DAY and TAYLOR (1949) for constant potential equipment. In making this comparison, the 1.5 mm beryllium inherent filtration used by the American workers may be taken as equivalent to 1.0 mm Be. plus 0.05 mm Al. in the corresponding data derived by the writer. Thus, the percentage deviation from the inverse square law for radiations spreading from 10 to 70 cms F. S. D. is 54 % and 29.5 % at 10 and 50 K. V. (constant) respectively, for zero external filtration. The corresponding losses at 10 and 50 K. V. P. (pulsating) for 0.05 mm Al. filtration, are found to be 59 % and 30.0 %. The ratios of these respective losses are 1.09 and 1.02, both points falling very close to the curve of figure 3, 2.

(3) The relative beam penetrations in »tissue», expressed in terms of half-value-depth (H. V. D.), under the two types of generation, are more difficult to derive from a theoretical standpoint. Transmission calculations for »tissue» would be straight-forward (as for H. V. L. derivations), but the problem is complicated by the effect of scattered radiation contributions. To overcome this difficulty, the relation between H. V. L. in aluminium and H. V. D. in »tissue» must be known, and the relevant data is given in figure 24 of the writer's above mentioned publication (p. 472). Combining this data with that of the curve for aluminium of figure 3, 1, an estimate of the relative H. V. D.'s under constant and pulsating tension (C. P./P. T.) has been derived, and is given in figure 3, 3. The filtration independence presumably holds to a first approximation.

No comparable H. V. D. data applicable to constant potential equipment is available, and the relatively small ratio (C. P./P. T.) would probably be masked by media differences. However, the stroboscopic device, to which reference has previously been made, has been used for this comparison. By measuring H. V. D. for the »peak» radiations only, and then under static conditions, ratios providing points covering the range 10 to 50 K. V. (P.) have been obtained, and these all fall within 10 % of the curve (fig. 3, 3) values. Similarly, relative H. V. L. measurements have been made over the range 20 to 50 K. V. (P.), and equally good agreement obtained (fig. 3, 1).

It may be noted, in passing, that the theoretical work confirms that the departure from linearity of the relation between output and tube current[1] (for a given F. S. D., K. V. P., and filtration) under pulsating tension results from the variations in K. V.- and tube current waveforms observed. On the other hand, the theory does not explain the presence of the double bend in the measured curves of H. V. L. against

[1] JENNINGS, Acta radiol. 33, pp. 452—454.

external filtration, both in aluminium, for a given K. V. P.[1] However, similar, though smaller, bends in the corresponding experimental curves for »tissue» penetration were also found, and OOSTERKAMP (1950) has recently reported finding similar bends in corresponding measurements with a Philips Contact Roentgen-ray Unit.

The Relative Merits of Constant and Pulsating Tension Generation

In using a beryllium window tube, it has been shown above that the relative outputs under constant and pulsating tension depend markedly on K. V. and filtration, the former method producing significantly increased outputs for low K. V.'s and low filtration, though this advantage is partly off-set by the maximum tube current ratings respectively applicable. From the standpoint of relative quality and beam penetration, under the two types of generation, the respective ratios are small. Moreover as these latter factors can be deliberately varied over specified ranges, such small ratios are of no significance.

The real advantage of constant potential, however, is in the calibration of a Unit for clinical use, for it is then possible to provide a calibration for a thimble chamber, from a free-air standard, which will be reliable. With pulsating tension equipment on the other hand, wave-form variations clearly lead to increased difficulties in calibration. Against this must be set the uneconomical size (from the commercial standpoint) of the condensers and transformer required to give a smooth output over the full range of 10 to 50 K. V. with a current drain of up to 50 mA. Thus, unless part of the K. V. or tube current ranges are sacrificed, approximately constant potential equipment is likely in practice to entail the presence of an appreciable K. V. »ripple». With decrease in K. V., this ripple will increase in magnitude, possibly up to 100 % if a tube current of 50 mA is used, thereby leading to an additional undesirable variable — the dependence of quality on tube current. For such reasons, the existing commercial designs of low kilovoltage roentgen-therapy Units fitted with beryllium window tubes (known to the writer) all employ pulsating tension.

It is hoped to publish an account of the theoretical work referred to above at a later date, together with a detailed comparison of the results so derived with the previously reported experimental ones.

Acknowledgements

Thanks are due to Dr. F. BUSH and Professor J. E. ROBERTS for their continued interest in this work; and to Mr. E. J. STEADMAN, of Messrs. Watson & Sons (Electro-Medical) Ltd., for his help in the wave-form measurements.

[1] JENNINGS, Acta radiol. 33, pp. 469—473.

SUMMARY

The results of an unpublished theoretical analysis (by the writer) are used to compare the respective roentgen radiation outputs and qualities under pulsating and constant potential generation, of a beryllium window tube operated over the range 10—50 K. V. (P.). An earlier comparison between some measurements made by the writer and some due to C. B. Braestrup are re-interpreted.

ZUSAMMENFASSUNG

Das Resultat einer unveröffentlichten theoretischen Analyse (des Verfassers) wird dazu benutzt, die Röntgenstrahleneffekte und Qualitäten, bei pulsierender und konstanter Hochspannung, einer Röhre mit Berylliumfenster bei 10—50 KV zu vergleichen.

Ein früherer Vergleich zwischen einigen Messungen, ausgeführt vom Verf., und einigen von C. B. Braestrup ausgeführten wird erneut besprochen.

RÉSUMÉ

Les résultats d'une analyse théorique antérieure (faite par l'auteur mais non publiée) sont employés en vue de comparer, en quantité et en qualité, les radiations radiologiques respectives durant une génération de potentiel, soit alternante, soit constante, à l'aide d'un tube à fenêtre de béryllium opérant sur l'espace de 10—50 kv. (C.). Une comparaison précédente entre les mensurations de l'auteur et d'autres dûs à C. B. Braestrup est réinterprétée.

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FROM THE ROENTGEN DEPARTMENT (DIRECTOR: PROF. Å. ÅKERLUND) AND THE DEPARTMENT OF WOMEN'S DISEASES (DIRECTOR: PROF. A. WESTMAN), KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN

ROENTGEN DIAGNOSIS OF TUBERCULOUS ENDOMETRITIS[1]

by

Kristina Ekengren and *Åke B. V. Rydén*

The outstanding feature of tuberculosis of the female genital organs seems to be its latency. The majority of the affected women have no symptoms and no palpable lesions of the pelvic viscera (RABAU, HALBRECHT and CASPAR, 1943; HALBRECHT, 1946; RYDÉN, 1950, JEDBERG, 1950, LILJEDAHL and RYDÉN, 1951, and others). In most cases sterility is the only complaint which causes these apparently healthy women to seek medical advice. In order to find out its cause they are examined by hysterosalpingography. It has been found that sterility is due to tuberculosis of the female genital organs in about 10 per cent of cases (LILJEDAHL and RYDÉN, 1951). For this reason it is important that special attention be given to the cases in which the hysterosalpingographic picture shows features which are suggestive of a tuberculous etiology.

According to MAGNUSSON (1945, 1947), MADSEN (1947), KO-CHI SUN (1948), DEUEL and DEUEL-ZOGG (1948), FREDRIKSSON (1949) and JEDBERG (1950) tuberculous salpingitis gives rise to a typical hysterogram. In a study of a large number of cases (EKENGREN and RYDÉN, 1950) we were able to distinguish various types of hysterosalpingogram which were characteristic of tuberculosis of the Fallopian tubes.

MADSEN (1947) wrote: ». . . tuberculous changes in the endometrium generally do not develop so far that they may be reckoned to appear in the hysterogram . . .». As a matter of fact, this happened in only two of his cases: ». . . the contours of the uterus were very irregular, in several places they were dentate . . .».

KO-CHI SUN (1948) claimed the following roentgenological features to be characteristic of tuberculosis of the uterus: ». . . the uterus appeared

[1] Submitted for publication, July 9, 1951.

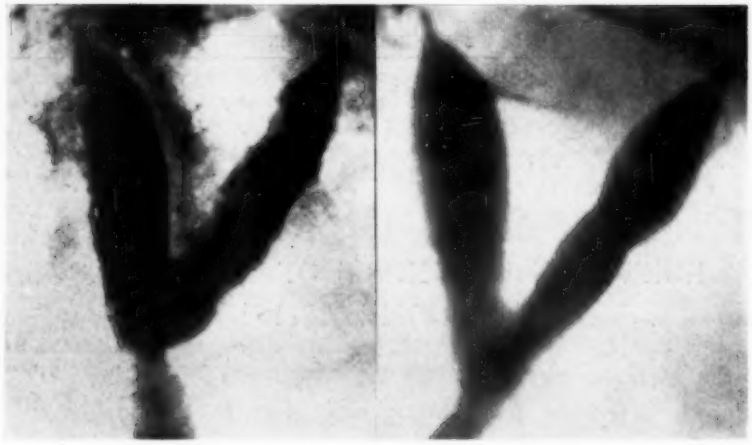

Fig. 1 a. Fig. 1 b.

Fig. 1. Tuberculous endometritis. a. Hysterography 19. 3. 1949. b. Same patient 7 months later after antibiotic treatment.

like a trumpet or a Voorhees' balloon, and its borders were shaggy and jagged. Its fundic shadow was invariably convex and its lateral contour likewise bulging». JEDBERG (1950), in 12 cases of tuberculous endometritis, found 7 cases in which the hysterographic findings were positive: »... the endometrial relief was irregular, raggy and saw-toothed ...». In two of these »... the cavity was small, narrow and deformed with fistula-like processes and lacunae».

In this present study an attempt was made to find out the roentgenological features which would be diagnostic of a tuberculous endometritis.

It covers 61 women with tuberculous endometritis treated in the Department of Women's Diseases of the Karolinska Sjukhuset in Stockholm between 1940 and 1950. In all these cases the clinical diagnosis was microscopically verified and each patient was examined by hysterosalpingography on one or several occasions. The control series comprised 149 women who were subjected to this examination in the above department during the last five years. In all cases the entire endometrium was microscopically examined either after curettage or hysterectomy; in none of them was there microscopic evidence of tuberculous endometritis.

In the 61 cases of tuberculous endometritis studied, the roentgenological appearance of the uterine body departed from the normal in 12 cases. (The roentgenological appearance of the isthmus and the cervix

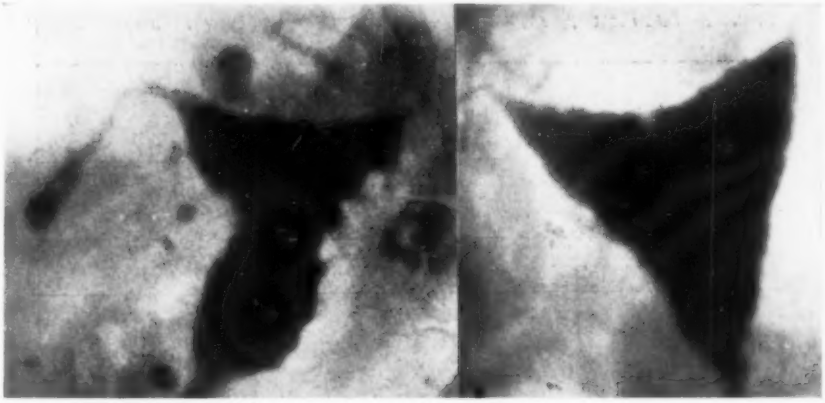

Fig. 2. Fig. 3.

Figs. 2—3. Tuberculous endometritis.

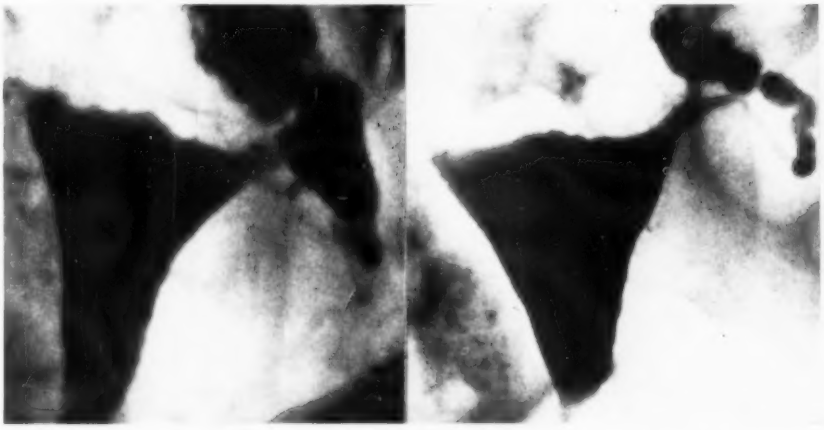

Fig. 4 a. Fig. 4 b.

Fig. 4. Tuberculous endometritis. a. Hysterography 31. 3. 1948. b. Same patient 10 months later after antibiotic treatment.

will not be discussed in this paper). The following types of roentgenological features were distinguished:

Type 1. Polyps of the uterine body or a polypous and hyperplastic endometrium (4 cases).

Type 2. Ragged or jagged saw-toothed uterine contours; absence of strictures (4 cases, Figs. 1 a, 2, 3, 4 a, 4 b).

Fig. 5. Cystic glandular hyperplasia. Ragged contours.

Fig. 6. Atrophic endometrium. Ragged contours.

Fig. 7. Normal endometrium. Ragged, saw-toothed contours.

Fig. 8. Tuberculous endometritis (Calcification in the right ovary).

Type 3. Recesses and fistulae leading from the uterine cavity; absence of strictures (1 case, Fig. 8).

Type 4. Evidence of strictures in the uterine cavity with fistulae and recesses leading to the myometrium (4 cases, Figs. 12, 13, 14 a—c, 17).

Discussion

Before discussing the above features the answers to the following two questions must be sought: 1) Which feature is or which features are suggestive of a tuberculous etiology? 2) Is one of them sufficiently characteristic to permit of a definite diagnosis?

Fig. 9.

Fig. 10.

Figs. 9—10. Two cases of internal endometriosis.

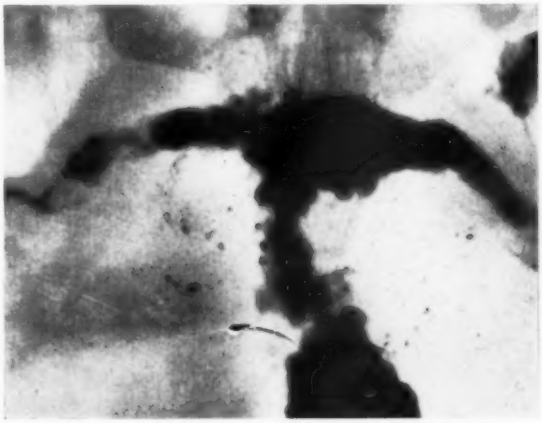

Fig. 11. Internal endometriosis suggested. Normal endometrium found at curettage (Remnants of iodized oil from previous hysterography).

Type 1. These features were encountered in the control cases in which they were much more frequently seen than among the patients with tuberculous endometritis. None of these features seems to be typical of the disease.

Type 2. These features may be of a tuberculous etiology. This assumption is supported by the observation made in one of our own cases (Fig. 1 a) in which they were very marked; after treatment with antibiotics, which cleared up the tuberculous endometritis, they were no longer visible in the roentgenogram (Fig. 1 b). In another case, how-

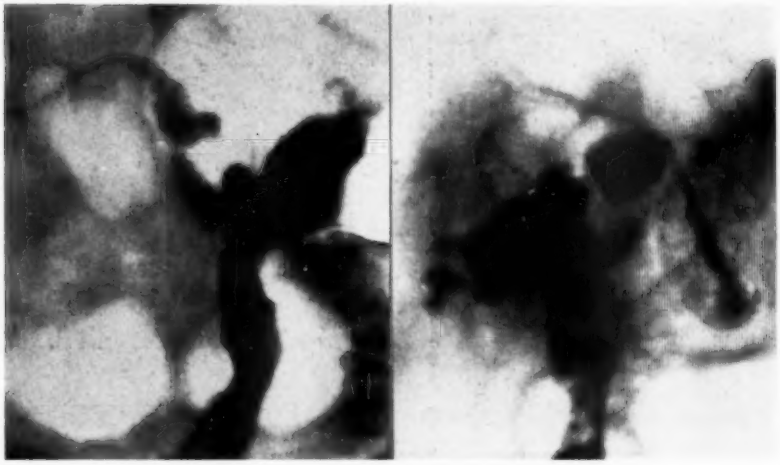

Fig. 12. Fig. 13.

Fig. 12—13. Tuberculous endometritis.

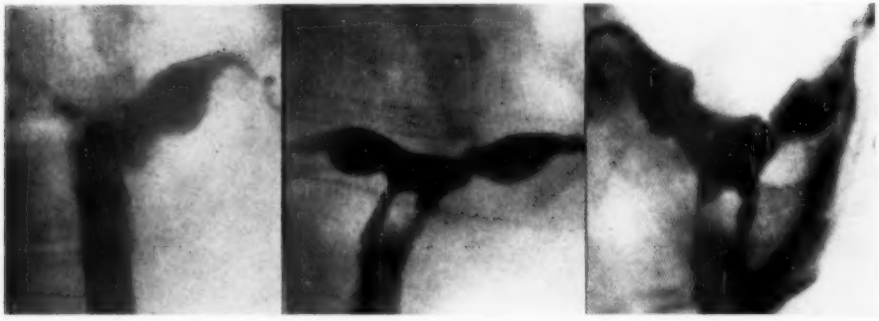

Fig. 14 a. Fig. 14 b. Fig. 14 c.

Fig. 14. Tuberculous endometritis. a. Hysterography 17. 8. 1946. b. Same patient $2^1/_2$ years later after antibiotic treatment. c. Same patient 6 months later.

ever, in which they were less marked and treatment with antibiotics also resulted in overcoming the tuberculous endometritis, they persisted (Figs. 4 a, 4 b).

Among the controls these features, though less marked, were observed in 3 cases (Figs. 5, 6 and 7). In none of them was there evidence of tuberculous endometritis.

If these roentgen manifestations are very marked the possibility of

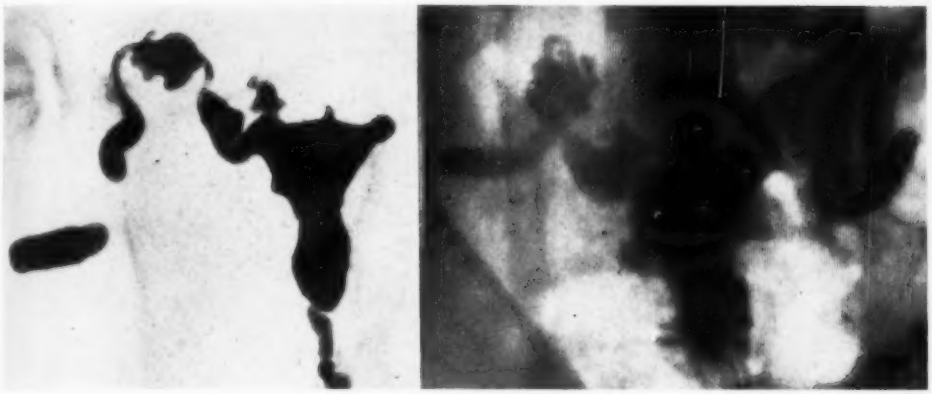

Fig. 15 a. Fig. 15 b.

Fig. 15. Healed tuberculous endometritis. a. Hysterography 25. 9. 1945 (iodized oil). b. Same patient 1½ year later (watersoluble contrast).

a tuberculous etiology should be considered but they are not definitely diagnostic of endometrial tuberculosis.

Type 3. A hysterogram of this type gives rise to the problem of differentiating between tuberculous endometritis, which causes recesses and fistulae leading to the myometrium, and internal endometriosis. Among the controls there was one case (Fig. 11) in which internal endometriosis was suggested; a microscopic examination of the myometrium was not carried out. For purposes of comparison, the roentgenological findings in two cases of internal endometriosis are shown in which the diagnosis was histologically verified (Figs. 9 and 10).

The differential diagnosis between these two conditions, however, cannot be made with certainty from this type of hysterogram.

Type 4. These features are very characteristic of tuberculous endometritis. Among the controls they were seen in two cases which will be briefly reported.

Case 1. The patient, aged 24, sought medical advice because of sterility. In 1945, she was examined by hysterosalpingography with an iodized oil as contrast medium (Fig. 15 a). In 1947, she was again examined by hysterosalpingography with a watersoluble contrast medium (Fig. 15 b). A subsequent curettage did not reveal any signs suggestive of endometrial tuberculosis. In 1948, a laparotomy was carried out which disclosed that both adnexa were fixed by adhesions and that the Fallopian tubes were occluded at their abdominal ends. Partial bilateral salpingectomy together with salpingostomy were carried out. The histological examination of the tubal specimens removed at the operation did not reveal anything suggestive of tuberculosis.

Case 2. This patient was 27 years old. In 1948, she was submitted to a diagnostic curettage because of sterility and irregular menstruation. The histological examination

Fig. 16. Healed tuberculous endometritis.

Fig. 17. Tuberculous endometritis.

revealed a non-specific endometritis. Another two curettages, one carried out in 1949 and the other one in 1950, did not disclose any tuberculous changes. Inoculation into guinea-pigs also gave negative results. In 1950, the patient was examined by hysterosalpingography. The findings are shown in Fig. 16.

Comments. In case 1, inflammatory processes involving both Fallopian tubes were found at laparotomy. The roentgenological appearance of the tubes prior to the operation corresponded to that which according to our experience (EKENGREN and RYDÉN, 1950) is seen practically only in cases of old tuberculosis of the Fallopian tubes, indicating that the tuberculous process is in an advanced stage of healing. In addition, there was evidence of calcification in one ovary. From these features the diagnosis »healed tuberculosis of the Fallopian tubes and the uterus» can be made with certainty.

In case 2, the roentgenological appearance of the tubes was also strongly suggestive of an old tuberculous lesion. In addition, a calcification was found in the left ovary. On the basis of these findings the definite diagnosis »healed tuberculous endometritis» is justified.

A hysterogram corresponding to type 4 is encountered in cases in which the tuberculous process also involves the myometrium. As this happens very rarely it is seen only in odd cases. It is characterized by a uterine cavity showing multiple strictures which are mostly seen in the uterine horns and often co-exist with intramural fistulae and recesses. The latter are also observed in internal endometriosis but in this condition strictures are absent. Moreover, this type of hysterogram occurs only

in cases in which the tuberculous lesion is of old standing. In one case of this series (Fig. 12) the tuberculous endometritis was diagnosed and verified 7 years before the patient was examined by hysterography. Roentgen evidence of changes in the uterus seems to indicate in these cases that the tuberculous inflammation is in an advanced stage of healing. In the case in which treatment with antibiotics resulted in overcoming the tuberculous endometritis, several control hysterographies furnished evidence that the strictures were more marked (Figs. 14 a—c). Moreover, in all cases of this series, the roentgenological appearance of the Fallopian tubes corresponded to that which, as mentioned before, we have found to be typical of long-standing tuberculosis of the tubes which is in an advanced stage of healing (EKENGREN and RYDÉN, 1950).

The roentgenological features of tuberculous salpingitis are much more characteristic than those of tuberculous endometritis. If the features of the hysterogram are suggestive of a tuberculous endometritis and correspond to those classed as type 2, this possibility can be safely ruled out, provided the tubes are normal, roentgenologically; tuberculous endometritis without coexisting or antecedent tuberculous salpingitis does not exist. If, however, the salpingogram shows the features which indicate tuberculous salpingitis, the suspicion of tuberculous endometritis is well founded.

SUMMARY

In a study of 61 women with tuberculous endometritis the following observations were made:

The lesions produced by tuberculous endometritis are roentgenologically visible only exceptionally.

Only in cases in which the tuberculous process involves the myometrium, which happens very rarely, is the hysterographic picture definitely diagnostic of tuberculous endometritis. The picture is characterized by a uterine cavity showing strictures which are mostly localized in the uterine horns and often coexist with fistulae and recesses leading to the myometrium.

The roentgen manifestations indicate in these cases that the tuberculosis of the uterus is of long-standing and in an advanced stage of healing.

ZUSAMMENFASSUNG

Beim Studium von 61 Frauen mit tuberkulöser Endometritis wurde folgendes beobachtet:

Schädigungen, hervorgerufen durch Endometritis tuberculosa, sind nur ausnahmsweise röntgenologisch sichtbar.

Nur in den Fällen, wo der tuberkulöse Prozess in das Myometrium eindring — und das geschieht selten —, gibt das hysterographische Bild definitiv die Diagnos einer tuberkulösen Endometritis. Das Bild ist karakterisiert durch eine Uteruskavität mit Strikturen, welche meistens in der Nähe der Tubenöffnung gelegen sind und oft zusammen

mit Fisteln und Ausbuchtungen in das Myometrium hinein auftreten. Die röntgenologischen Veränderungen in derartigen Fällen zeigen, dass die Uterustuberkulose schon lange bestanden hat und sich im Stadium fortgeschrittener Heilung befindet.

RÉSUMÉ

Les observations suivantes ont été faites dans une étude sur 61 femmes atteintes d'endométrite tuberculeuse.

Les lésions provoquées par l'endométrite tuberculeuse ne sont que rarement visibles à l'examen radiologique.

Ce n'est que dans les cas ou le processus engage le muscle utérin, cas exceptionel, que l'hystérographie radiologique donne le diagnostic certain d'endométrite tuberculeuse. L'image est caractérisée par une cavité utérine montrant des strictions, spécialement au niveau des cornes et qui s'accompagnent souvent de fistules et de poches qui pénètrent le muscle. L'image radiologique montre dans ces cas que la tuberculose de la matrice est ancienne et en bonne voie de guérison.

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AUS DER RÖNTGENABTEILUNG (CHEFARZT: DR. SIGFRID ARNELL) UND DER CHIRURGISCHEN ABTEILUNG (CHEFARZT: DR. OSKAR LINDÉN) DES ZENTRALLAZARETTES GÄVLE, SCHWEDEN.

MULTIPLE PROSTATA- UND URETHRASTEINE ALS FOLGE VON UROGENITALTUBERKULOSE[1]

Beitrag zur röntgenologischen Differentialdiagnose von Prostatakonkrementen

von

Gustaf Notter

Wenn Urethrakonkremente heute für den Urologen kein seltenes Vorkommnis mehr sind (2 ‰ der urologischen Pat.), ist das ein Verdienst der besonders durch die Röntgenuntersuchung verbesserten Diagnostik. GUYON lehrte z. B. 1888 in seinen Vorlesungen, dass ihm in 20 jähriger Praxis kein einziger Fall begegnet sei. Doch sind Urethrasteine für den »Nicht-Urologen» immer noch so relativ selten und verbergen sich diagnostisch zuweilen unter so diffusen Beschwerden, dass eine Veröffentlichung dieses Falles gerechtfertigt erscheint.

Was man gemeinhin Prostatasteine nennt, ist ein Sammelbegriff für genetisch sehr verschiedene Dinge. Man unterscheidet:

1. Endogene = primär in der Prostata gebildete Konkremente,

a) Korpuskula amylacea. Sie sind im Parenchym belegen, konzentrisch geschichtet und radiär gestreift. Hauptanteil ist das Lezithin. Im Anfang rundlich, können sie später durch Kalkanlagerung die Form verändern.

b) infolge geweblicher oder kolloidosmotischer Veränderungen in der Prostata. (Hypertrophie, zunehmendes Alter usw.)

c) durch kalkige Inkrustation von Gewebsnekrosen in chronischen Prostatakavernen.

2. Exogene = sekundär in die Prostata gelangte Steine,

a) aus den Urinwegen. Hierzu rechnen auch Divertikelsteine der Pars prostatika Urethrae, die durch entzündliche Gewebseinschmelzungen in die Prostata gelangen können.

[1] Bei der Red. am 18. V. 1951 eingegangen.

b) aus den Samenwegen. (Glandulae seminales und Ductus deferens.)

Die Urethrasteine teilt man ein in:

1. Endogene = an Ort und Stelle entstandene Steine

a) in Divertikeln. Dabei ist es klinisch ohne Bedeutung ob es sich um »wahre» Divertikel (Wandschichten aus Muskularis und Mukosa) oder um »falsche» (Wandschicht nur aus Mukosa) handelt. Selbst histologisch kann eine Trennung nach Entzündungen unmöglich sein. Auch ist in manchen Fällen nicht zu entscheiden, ob der Stein z. B. in ein primäres Divertikel eingeschwemmt wurde oder das Divertikel sich erst sekundär um den Stein herum gebildet hat. Überwiegend liegen die Divertikel an der dorsalen Urethrawand, weil die Muskularis hier am schwächsten ist.

b) nach Traumen. Auf 10 Verletzungen kommt ein Stein!

2. Exogene = aus den oberen Urogenitalwegen eingeschwemmte Steine.

3. Paraurethralsteine.

90 % aller Urethrasteine stammen aus den oberen Harnwegen, wenige aus den Samenwegen und, dem Schrifttum nach zu urteilen, noch weniger aus einer nekrotischen, tuberkulösen Prostata wie in dem eigenen Falle.

Schon beim Neugeborenen werden Urethrasteine in der Fossula prostatika gefunden, die hier bereits so gross wie eine Erbse sein kann. An dieser Stelle zwischen Kollikulus seminalis und Orificium Urethrae internum gibt es zuweilen tief in die Prostata hineinreichende Schleimhautduplikaturen, die zur Steinbildung praedestinieren. Auch der Utrikulus maskulinus, die »männliche Vagina», die beim Säugling noch die ganze Prostata durchsetzt, kommt hierfür in Frage. Beim weiblichen Geschlecht bestehen durch mangelhafte Rückbildung embryonaler Anlagen ähnliche Schleimhauttaschen.

Die Steine liegen vorwiegend in den physiologischen Engen der Urethra, Pars diaphragmatika, — kavernosa und Orificium externum, wo sie beim Durchgang hängen bleiben, oder sie stauen sich vor diesen Engen in der Pars prostatica, distal des Bulbus Korporis kavernosi und in der Fossula navikularis, sowie in den sich blasenwärts jeder Striktur bildenden Erweiterungen. Auch die Ausweitung und sagittale Abknickung des suprakollikulären Urethrateiles bei der Prostatahypertrophie wirkt funktionell in gleicher Weise. Die Steine können teilweise ins Blasenlumen hineinreichen und führen so zu Sphinkterinsuffizienz, Harnträufeln und Zystitis.

Die Paraurethralsteine liegen meist symptomlos in der Pars bulbosa und — prostatica. Nur bei Missbildungen kommen sie auch in der Pars kavernosa vor. (Hypospadie.)

Abb. 1. Bohnengrosser Stein im re. Ureter kurz vor der Einmündung in die Blase. Ausserdem einzelne linsengrosse Prostatakonkremente vom Typus I.

Abb. 2. Derselbe Fall. 10 Monate später. Der Stein liegt jetzt in der Pars prostatica und verursacht bedeutende Miktionsbeschwerden und makroskopische Hämaturie.

Zahlreich sind die *Theorien* über die Steinbildung in den Harnwegen. Als Ursache nimmt man an: 1. Ein. Störung des Gleichgewichtes zwischen den Muzinkörpern des Harns und den stabilen Kolloiden Chondroitinschwefelsäure und Nukleinsäuren, die die schwerlöslichen Stoffe adsorbieren und ein Ausfallen verhindern. Ausserdem hemmen sie bei tropfiger Entmischung die Kristallisation. 2. Eine Störung der Grenzflächenspannung Urin—intakte Schleimhaut bei Entzündung, bakterieller Zersetzung des Harns und Nekrose. Als Salzfänger und Steinkerne dienen Gewebsteile, Blutbestandteile, Bakterienhaufen, Fremdkörper und ev. im Überschuss zugeführte Medikamente. Unter den Bakterien kommt insbesondere der Staphylokokkus albus in Frage, welcher durch sein Vermögen Harnstoff zu spalten ein günstiges Milieu zum Ausfällen von Alkalien schafft. (Hellström.)

Die Harnsteine enthalten zumeist 5—20 % Eiweiss als Gerüstsubstanz. Wahrscheinlich flocken zuerst die mukoiden Kolloide aus, in die sich sekundär Salze inkrustieren. Die grosse Grenzflächenspannung dieses Eiweisskernes fördert den weiteren Niederschlag der Salze. Jede funktionelle und organische Harnstagnation begünstigt die Steinbildung. Die Konzentration der Steinbildner selbst spielt nur eine untergeordnete Rolle. Man weiss, dass geologische und geographische Umweltsfaktoren, Rasseeigentümlichkeit, Konstitutionstyp, Diätkost, Krankheiten wie Gicht, Tabes, Tuberkulose und selbst Diathesen wie

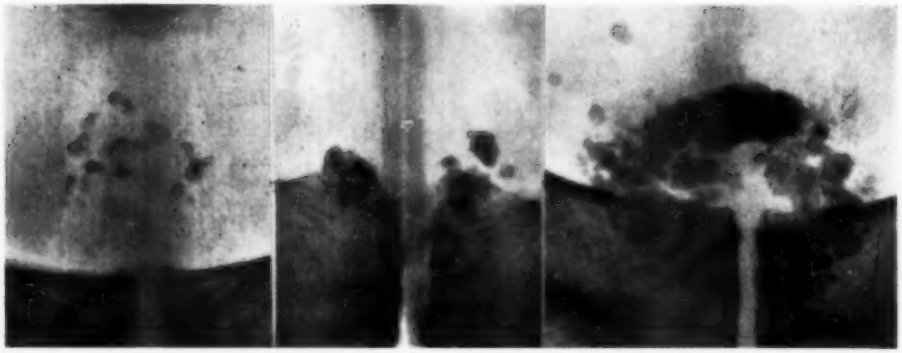

Abb. 3. Abb. 4. Abb. 5.

Abb. 3. Typische Prostatakonkremente vom Typus I bei einem 59 jähr. Pat.

Abb. 4. Grössere Konkremente vom Typus I bei einem 42 jähr. Pat. Deutlich sichtbare körnige Struktur und Konturen.

Abb. 5. Starke Konkrementbildung vom Typus I. 58 jähr. Mann. In der Jugend Go. und Lues. Seit 12 Jahren chronische unspezifische Prostatitis mit Pyurie, Bakteriurie und mässiger Hämaturie. Prostata leicht vergrössert, fest, glatt, und gut abgrenzbar.

Oxalurie, Phosphaturie und Uraturie bei der Steinbildung keine *kausale* Rolle spielen. Eine Auflösung von Steinen ist in vereinzelten Fällen beschrieben und wird auf Behebung der Stase und Ansäuerung des Harns zurückgeführt.

In 66 % aller Ca-Steine liegt eine erhöhte Ca-Ausscheidung ohne erhöhten Ca-Blutspiegel vor. Einfluss auf die Ca-Ausscheidung und Umsetzung haben parathyreoide, hypophysäre, renale und auch allergische Faktoren, weiter Skeletterkrankungen, lange Immobilisation bei Frakturen, Vit. D und das Ca : P-Verhältnis. Bei *Prostatasteinen* handelt es sich vorwiegend um Parenchymverkalkungen und liegen daher andere Verhältnisse vor.

Die *Röntgenuntersuchung* gibt Auskunft über Lokalisation, Grösse, Anzahl und Form der Steine. Die qualitative Diagnose auf Grund wechselnder Absorptionsgrösse der Salze ist praktisch von geringer Bedeutung. Dagegen lassen Form, Grösse und Struktur der Steine manchmal eingehendere Schlüsse auf die Genese zu. Aus den Nieren ausgespülte Steine haben oft ovale abgerundete Form, können in der Blase durch Kalk und Salzablagerungen zu grossen runden geschichteten Steinen anwachsen, manchmal aber auch bis in die Pars prostatika Urethrae gelangen und hier leicht mit Prostatasteinen verwechselt und übersehen werden. (Abb. 1 und 2.) Man tut im Falle von Nephrolithiasis und medial belegenen Prostatakonkrementen gut, sich dieser Möglichkeit zu erinnern.

Bei der Betrachtung von Prostatakonkrementen kann man röntgenologisch hauptsächlich 3 Typen unterscheiden, die sich nicht ohne weiteres in das pathologische Schema eingliedern lassen.

Abb. 6. Multiple Konkremente vom Typus II in der Prostata. Beachte die mit einem Pfeil bezeichneten Konkremente in der Urethra.

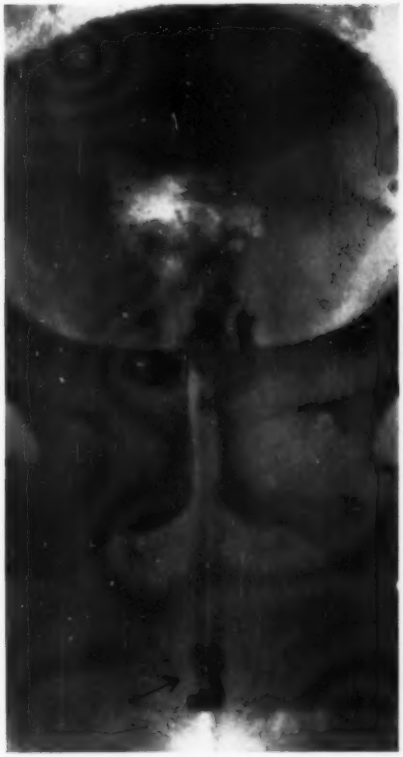

Abb. 7. Derselbe Fall. Ein Jahr später. A-p Bild. Bedeutend weniger Konkremente in der Prostata. Die Urethrakonkremente liegen weiter distal. Die alten Konkremente sind abgegangen und neue sind an ihre Stelle getreten.

Typ I beginnt mit anfangs kaum sichtbaren, feinen, punktförmigen Verkalkungen (Abb. 3), die allmählich grösser werden und zu kleinen Rasen zusammenfliessen (Abb. 4). Sie behalten aber immer ihre granulierte Struktur und Kontur bei und bilden nur selten grössere kompakte Steine. Diese Verkalkungen werden bei manchen Patienten bereits vor dem 30. Lebensjahre röntgenologisch sichtbar und werden im Anfang wegen ihrer geringen Dichte und der sie überdeckenden Symphyse meistens übersehen. Sie wachsen im Laufe der Jahre nur sehr langsam. Ihr Auftreten steht in keiner Beziehung zur Bildung von Phlebolithen, arteriosklerotischen Gefässverkalkungen oder allgemeiner Osteoporose, abgesehen

Abb. 8. Schrägaufnahme der Urethra bei derselben Untersuchung. Die Pfeile bezeichnen die Weichteilkonturen des Penis. Mindestens 6 Konkremente in der Pars cavernosa sichtbar, das Grösste am weitesten distal, die Proximalen perlschnurartig hintereinander gestaut. Weiter oben die auf Abb. 7 besser sichtbaren Prostatakonkremente. ↗ bezeichnet die Verkalkung in der li. Epididymis.

von der physiologischen Anhäufung dieser Erscheinungen im Alter. Das im allgemeinen gehäuftere Auftreten der Konkremente im Alter ohne klinische Beschwerden lässt annehmen, dass es sich hierbei um degenerative Gewebsveränderungen im Prostataparenchym handelt, die ohne Entzündungserscheinungen entstehen. Wie weit sie auf hypertrophischen bzw. atrophischen Gewebsveränderungen und kolloidosmotischen Umstellungen im Alter beruhen, ist patho-physiologisch noch nicht geklärt. Trifft man aber auf eine Vielzahl von Konkrementen gleichen Typs bereits in jüngeren Jahren, so liegt fast immer eine jahrelange chronische Prostatitis mit allen klinischen Symptomen vor (Abb. 5). Die Relation zwischen Alter des Patienten und Menge der Konkremente ist hier für die Beurteilung wichtig.

Beim *Typus II* finden sich dagegen Konkremente von der Art des weiter unten beschriebenen Falles (Abb. 6—11). Sie sind bis bohnengross, von wechselnder Dichte, und haben zackige Konturen. Die körnige Struktur des Typus 1 fehlt. Es handelt sich hierbei um Verkalkungen nekrotischen tuberkulösen Prostatagewebes.

Den III. Typ zeigen Abb. 12—13. Es sind dies Steine unklarer entzündlicher Genese, die ringförmig in der Prostata liegen. Sie sind bis erbsengross, rund, glatt und von gleichmässiger Dichte. Sie fanden sich im abge-

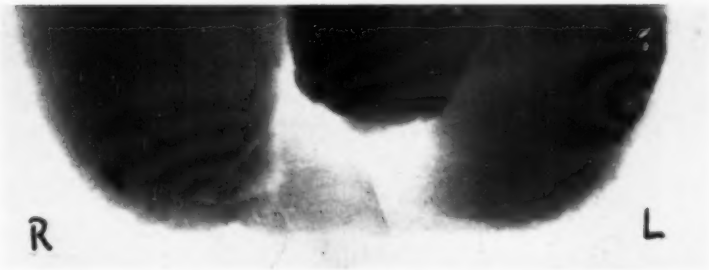

Abb. 9. Aufnahme des Scrotum. Mandelgrosse Verkalkung in der li. Epididymis. Rechts sieht man eine 3 mm grosse flache Verkalkung und die gewundenen Gänge des Ductus epididymidis auf eine Länge von 2—3 cm. In der Mitte der Weichteilschatten des Penis.

bildeten Falle bereits im Jahre 1943 und haben sich in den letzten 8 Jahren nur unbedeutend vergrössert.

Auch Mischformen aller 3 Typen kommen vor, wobei in höherem Alter meistens der Typ I hinzukommt.

Bei der Durchsicht von 1,000 männlichen Urographien verschiedenen Alters fanden sich Konkremente vom Typ I in 168 Fällen bei einem Durchschnittsalter von 54 Jahren. Typ II fand sich nur in einem Fall. Typ III fand sich in 5 Fällen, wenn auch nicht in so ausgeprägter Form wie auf Abb. 12—13. (In 2 Fällen lag doppelseitige offene Lungentuberkulose vor, in einem Fall eine Urogenitaltuberkulose. In jedem Falle bestanden Miktionsbeschwerden und intermittierende Hämaturie.)

Eine ausschliessliche röntgenologische qualitative Differenzierung in tuberkulöse und nicht tuberkulöse Konkremente entsprechend Typ II und III ist *nicht* möglich. Klinik und Laboratorium sind zur Diagnose unerlässlich. Doch ist der Röntgenologe berechtigt bei Prostatakonkrementen vom Typ II und III, sowie bei stark ausgeprägten Verkalkungen vom Typ I in jungen Jahren (Abb. 5), eine chronische Prostatitis bzw. eine Urogenitaltuberkulose zu vermuten und kann oft die Diagnose unklarer Urogenitalerkrankungen hierdurch klären helfen. Die vielfach vertretene Ansicht, dass Prostatakonkremente klinisch unwichtig seien, und oft in einem Röntgenbefund nicht einmal erwähnt werden, kann man nicht vertreten. Jahrelang intermittierende Hämaturien finden bei negativem Nieren- und Blasenbefund oft durch Prostatakonkremente ihre Erklärung.

Liegen Steine zur chemischen Analyse vor, erleichtert diese natürlich bedeutend die Klärung der Genese. Weiterhin ist die Feinschnittuntersuchung oder das Anschliffverfahren von Nutzen für die Erkennung der

Abb. 10. Urethrographie, Schrägaufnahme. Normale Blase mit geringer Impression von unten. Mässige Prostatavergrösserung. Pflaumengrosse tuberkulöse Kaverne in der Prostata dorsal von der Urethra (sichtbar auf der seitlichen Aufnahme). Konkremente nur undeutlich durch die Kontrastflüssigkeit hindurch sichtbar. Beachte die multiplen, unregelmässigen, flachen Wandverdickungen im vorderen Teil der Pars cavernosa: tuberkulöse Strikturen nach Urethritis (→). +→ bezeichnet verkalkte linke Epididymis.

Kernstruktur, angelagerter Schichten und des Kristallaufbaues. Die Analysenquarzlampe ermöglicht eine weitere Differenzierung mit ultraviolettem Licht. Durch die Kristallographie erklären sich auch Formveränderungen der Steine.

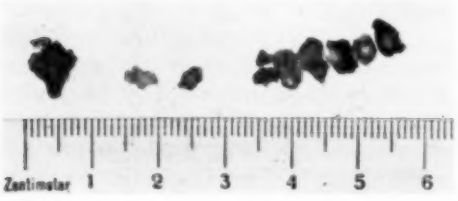

Abb. 11. Röntgenaufnahme der aus der Urethra entfernten Konkremente in natürlicher Grösse.

Wie NAKANO ausführt, gehören Urate, Phosphate, Zystin und Xanthin dem rhombischen Kristallsystem an und ihre Massenkristallisation zeigt flache Ellipsenform. Oxalate gehören dem quadratischen Kristallsystem an und haben Kugelgestalt. Die Kombination beider Gruppen ergibt die Eiform mit wechselndem Durchmesser, entsprechend dem mengenmässigem Verhältnis beider Arten. Wie im Mineralreich erfolgen auch in Harnsteinen Austausch-

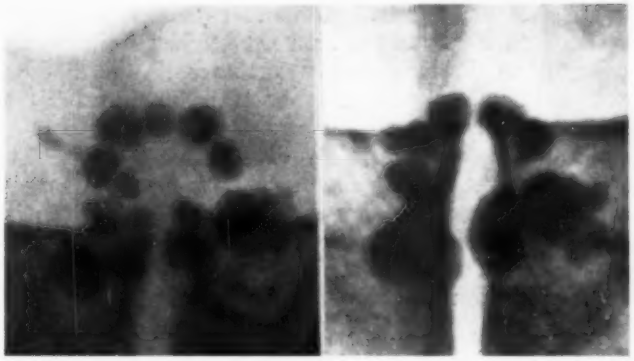

Abb. 12. Abb. 13.

Abb. 12. Prostatakonkremente vom Typus III mit auffallend abgerundeter Form, glatten Konturen und gleichmässiger Dichte. Keine körnige Struktur. Blasenübersicht 1943 bei 43 jähr. Mann. 1942 u. 43 Epididymitis re., Pollakisurie ohne Miktionsbeschwerden. Ausstrich und Kulturen auf Tb-Bazillen 3 mal neg. Prostata klein, hart, knollig, bei Druck schmerzhaft. Deutliche Krepitation von Prostatakonkrementen bei rektaler Untersuchung. Re. Epididymis knollig, hart und unempfindlich. Die Bildung solch grosser Prostatakonkremente bedarf längerer Zeit als nur 1 Jahres.

Abb. 13. Derselbe Fall wie Abb. 12 aber 8 Jahre später. Die Konkremente haben sich nur wenig vergrössert und haben ihre Lage nahezu unverändert beibehalten.

vorgänge (Metasomose). Mineralstoffe können dabei vollständig ihren chemischen Charakter verändern. Die Riss- und Spaltbildung in Harnsteinen erklärt man auf verschiedene Weise: CO_2-Entwicklung, Austrocknen, Bakterienwachstum und als Folge eines langsamen Umwandlungsprozesses, der mit der Entquellung der Steinanlagen beim Übergang aus der Kugelform in die Polyederform beginnt und am Ende zur Selbstzertrümmerung führt (K. H. Bauer).

Der grösste bisher gefundene Urethrastein war so gross wie der Kopf eines Neugeborenen. Ein anderer wog 1,020 g! Bei einem chinesischen Bauern fand Lai nicht weniger als 217 Steine! Farbe und Konsistenz wechseln mit der chemischen Zusammensetzung. Urate ziegelrot, Phosphate blassgelb usw. Oxalate, Urate und reine Karbonate sind sehr hart. Amyloid- und Fibrinsteine sind weich wie Bienenwachs. Seltenere Steine bestehen aus Zystin, Xanthin, Indigo, kohlensaurem Kalk und Amyloid. Meist handelt es sich um gemischte Steine mit Phosphat-Karbonatmantel.

Die durch die Prostatasteine verursachten *Symptome* sind sehr wechselnd. Die Steine können zeitlebens unbemerkt bleiben oder mit zunehmender Grösse zu lokaler Entzündung, Ulzeration, Abszess, Fisteln oder chronischen Kavernen führen.

Steine in der Pars prostatika können zu Wandersteinen werden, bleiben ev. in der Pars membranacea stecken und führen zu totaler Harnverhaltung, Stase, Zystitis und Pyelitis. In extremen Fällen zu Urethra-

ruptur, Harninfiltration, Sepsis, Pyämie und Urämie, bei Kindern manchmal zu Testis- und Penisgangrän. In zahlreichen Fällen wird der Stein spontan über einen Perinealabszess »geboren». Wie bereits erwähnt, findet die Divertikelbildung am leichtesten in der dorsalen Urethrawand statt und Abszesse und Fisteln entwickeln sich so zum Perineum hin. Bei der Frau imponieren Steinbeschwerden bei ungestörter Miktion daher oft als Vaginalbeschwerden mit einem Schwere- und Fremdkörpergefühl. Ev. perforiert der Divertikelsack in die Vagina. Die auf natürlichem Wege ausgeschwemmten kleineren Steine können die Schleimhaut verletzen und zu traumatischen Strikturen führen. Die weitaus häufigsten Beschwerden sind aber: Partielle und komplette Obstruktion. Langdauernde, rezidivierende Tenesmen bei der Miktion und im Sitzen. Dysurische Inkontinens. Blutig-eitrige urethrale Sekretion und cystitische Veränderungen im Urin. Als Störungen der Sexualsphäre beobachtet man häufige, schmerzhafte Pollutionen, Priapismus, Abnahme der Potenz und ev. Hämospermie. Bei rektaler Untersuchung ist die Prostata verhärtet und man tastet einzelne Steine oder deren Krepitation. Auch nach der Steinentfernung können die Beschwerden durch Entzündung und Striktur noch weiterbestehen.

Diese wechselnde Mannigfaltigkeit der Symptome leiten den klinischen Verdacht in manchen Fällen eher auf einen Ureterstein oder eine Prostatahypertrophie. Da die routinmässigen Bilder bei der i. v. Urographie oft mit der Symphyse nach kaudal hin abschliessen, entgehen dem Röntgenologen manchmal Prostatakonkremente und häufiger noch Urethrasteine und Verkalkungen im Nebenhodenbereich.

Behandlung: Urethrasteine entfernt man, wenn sie Beschwerden machen, denn sie können wachsen und in der Folgezeit zu schweren Komplikationen Anlass geben. Die Dehnungsfähigkeit der Urethra ist zwar enorm und Steine von 200 g und 1.3 cm Dicke sind spontan abgegangen! Festsitzende Steine können auch nach langer Zeit noch abgehen. Sehr grosse Steine können symptomarm sein, wenn sie kanalisiert sind. Man entfernt den Stein auf die schonendste Weise. Liegt er in der Pars prostatika, gelingt es ev. ihn in die Blase zurückzustossen und hier zu zertrümmern bzw. durch Sektio alta zu entfernen. Bei anderen gelingt die Ausziehung mit Hilfe des Urethroskopes oder die Entfernung mit Elektroresektion. In der Pars anterior wird man nach Dilatation der Urethra versuchen, am Konkrement vorbeizukommen und dieses dann herauszulöffeln. Mit Vorteil kann man hierzu auch die Zeiss-Katheterschlinge verwenden, wie sie zur Entfernung von tiefsitzenden Ureterkonkrementen gebräuchlich ist. In den hartnäckigsten Fällen bleibt die Meatotomie, Boutonnière oder die perineale Urethrotomie übrig. In manchen Fällen ist Prostatektomie indiziert, doch ist man bei alter Urogenitaltuberkulose

sehr zurückhaltend, um nicht ruhende Herde zu reaktivieren. Hier gibt man der medikamentösen Behandlung mit Antibiotika den Vorzug.

Eigener Fall:

64 Jahre alter Bauschreiner. 1 Tochter, geb. 1916. Freiwillige Sterilität in der Ehe bis 1924, danach keine Kinder mehr.

1916 beids. Epididymitis. Nach Abklingen der akuten Schwellung blieb eine kirschgrosse, harte, nunmehr schmerzlose Geschwulst in der li. Seite des Skrotum zurück.

1924 Nephrektomie re. wegen Nierentbc. Gleichzeitig bestanden damals eine tuberkulöse Zystitis und Ureteritis mit Ulzerationen in der re. Uretermündung. In der extirpierten Niere fanden sich 2 haselnussgrosse Kavernen und eine miliare Aussaat in der Rinde. Der Pat. überstand die Op. ohne Komplikationen bei gutem AZ. und erholte sich schnell.

Bis zum Sommer 1949 vollkommen beschwerdefrei. Dann kam die Miktion schwer in Gang, der Strahl wurde schwächer, Nachträufeln von Harn, keine mikroskopische Blutung. Manchmal reissende, zum Perineum und Rektum hin ausstrahlende Schmerzen nach der Miktion. Im Dez. 1949 stationäre Aufnahme in der Chir. Abteilung.

Die Prostata war sehr hart, knollig, gut abgrenzbar. Im Urin einzelne Erythr. und reichlich Leukoz. Rest-N 36 mg%. Eiweiss und Zucker neg. Kein Gewichtsverlust, guter AZ. Bei einer vorgenommenen Skelettkontrolle sah man auf dem Röntgenbild des Beckens (Abb. 6) in Höhe der Prostata in einem Umkreis von 4×4 cm multiple Konkremente von verschiedener Grösse mit unregelmässigen, gezackten Konturen und wechselnder Form. 3 cm unterhalb der Pars prostatika sah man ein ungefähr 0.1×0.5 cm grosses Konkrement gleichen Aussehens, das wahrscheinlich in der Harnröhre lag. Die genaue Lokalisation unterblieb und der Pat. wurde nach Hause entlassen, da während des klinischen Aufenthaltes keine Beschwerden mehr bestanden. Nach der Entlassung traten sie jedoch bald wieder auf. Nach kurzer totaler Harnverhaltung ging ein Stein spontan ab und blieb im Orificium externum stecken. Der Pat. zog ihn selbst aus der Harnröhre heraus. In der Annahme, dass nun alle Beschwerden behoben seien, suchte er den Arzt nicht mehr auf. Im Laufe des Jahres gingen eine ganze Anzahl Steine ab ohne makroskopische Hämaturie. Im Dez. 1950 vermehrte Schmerzen und erneute Klinikaufnahme.

Eine Sondierung der Urethra war nun nur bis zu einer Tiefe von 10 cm möglich. Hier spürte man auch von aussen in der Urethra eine erbsgrosse, druckempfindliche Verhärtung. Weiter dammwärts fanden sich 2 weitere Verhärtungen. Bei der i. v. Urographie arbeitete die kompensatorisch hypertrophierte li. Niere normal und zeigte keine pathologischen Veränderungen. Die Anzahl der Prostatakonkremente hatte sich seit dem 19. 12. 49 innerhalb des letzten Jahres bedeutend verringert. Höchstens ein Drittel der Steine war noch vorhanden (Abb. 7). Die 1.2 cm lange Verschattung unterhalb der Prostata erwies sich auf der Schrägaufnahme der Urethra (Abb. 8) als 7—8 Konkremente in der Pars cavernosa Urethrae, deren grösstes am weitesten distal lag. Urethra- und Prostatasteine haben gleiches Aussehen.

Beim Urethrogramm mit 20% Umbradil (Abb. 9) sieht man in Höhe der Pars prostatika eine auf der dorsalen Seite der Urethra gelegene, 20×25 mm grosse, ziemlich scharf begrenzte Kavität in der die beschriebenen Konkremente liegen. Man sieht keine Kontrastfüllung von Fisteln oder Drüsengängen wie bei einer Prostatitis unspezifischer Genese. Das Kollikelrelief ist nicht sichtbar. Der suprakollikuläre Teil der Urethra ist leicht sagittal abgewinkelt, starr, ungefähr 3.5 cm lang und 5 mm breit. Das normale Schleimhautrelief ist ausgelöscht. Der Blasenboden ist vor und hinter dem Orificium internum nach oben gedrängt wie bei mässiger Prostatahypertrophie. Die Konkremente in der Pars cavernosa sind durch den Kontrast hindurch nicht zu sehen. Der Kontrast liess sich ohne Widerstand in die Urethra injizieren, ein Zeichen, dass die normale Harn-

passage nahezu unbehindert war und erklärt die geringen Miktionsbeschwerden des Patienten. In den distalen 10 cm der Pars kavernosa finden sich flache, unregelmässige Wandverdickungen, die das Urethralumen stellenweise bis auf die Hälfte einengen. Diese Strikturen sind aufzufassen als Residuen einer abgelaufenen tuberkulösen Urethritis, die in 35 % aller Urogenitaltuberkulosen besteht. Gegen die ev. traumatische Genese (Steinabgang) spricht Form und Ausdehnung, da diese ringförmig, klappenartig und scharf begrenzt sind.

In der li. Seite des Skrotum sieht man eine 25 × 12 mm grosse Verkalkung, die sich aus einer Anzahl kleinerer und dichterer Körper zusammensetzt. Diese Verkalkung entspricht der Verhärtung in der li. Epididymis (Abb. 8, 9, 10). Auf der re. Seite ist der Duktus epididymidis auf eine Strecke von 2—3 cm verkalkt und deutlich mit seinen Windungen sichtbar. In dessen Nähe liegen 2 weitere kleine Verkalkungen. Vas deferens und Vesikula seminalis sind nicht sichtbar. Die Lungen haben erbsengrosse Verkalkungen im Parenchym und beiden Hili, sowie eine Pleuraschwarte re. als Zeichen abgelaufener Lungentuberkulose und Pleuritis.

Die Urethrakonkremente wurden nach Dilatation forcée mit Guyonsonden bis No. 21 in Lumbalanaesthesie extrahiert (Dr. Gibson). Die Sonde konnte nur 10 cm tief eingefürt werden und stiess dann auf ein Hindernis. Nachdem ein erster Versuch mit stumpfen Löffeln missglückte, gelang die Extraktion mit Leichtigkeit mit Hilfe einer Zeisskatheterschlinge. Alle Urethrakonkremente wurden entfernt, zum Teil in Fragmenten. Beim anschliessenden Sondieren der Blase spürte man in der Pars prostatika deutliches Schaben an den dort noch liegenden Konkrementen.

Die path.-anatomische Diagnose von Gewebsteilen aus der Urethra ergab keinen Anhalt für tuberkulöse Erkrankung. Die biologische Meerschweinchenprobe mit Urin war jedoch positiv.

Die Steine hatten eine gelb-braune Farbe, waren sehr hart, spröde, hatten eine sehr zerklüftete, rauhe und scharfe Oberfläche ohne Schlifffläche und waren nicht hohl. Diese vom gewöhnlichen Bild eines Urinkonkrementes abweichenden Eigenschaften stellten die Frage nach der Entstehung der Konkremente. Da die Steine nicht aus den oberen Harnwegen stammten und keine Korpora amylacea oder Divertikelsteine waren, war es am wahrscheinlichsten, dass sich die Konkremente als kalkige Inkrustation um tuberkulöse Gewebssequester in der auf dem Urethrogramm sichtbaren Prostatakaverne gebildet haben und von dort aus allmählich in die Harnröhre gelangt sind.

Diese Auffassung bestägtigte auch die chemische Analyse, die im Medizinisch-chemischen Institut der Universität Uppsala (Chef: Prof. Dr. Gunnar Blix) ausgeführt wurde. »Die Konkremente bestehen hauptsächlich aus Kalziumtriphosphat und etwas Kalziumkarbonat. In Form, Farbe und Härte weichen sie sehr von gewöhnlichen Urinkonkrementen ab. Auch fehlen die für diese karakteristischen Beimengungen von Tripelphosphat und Ammoniumurat. Eine geringe Menge von Kalziumoxalat deutet daraufhin, dass die Konkremente wenigstens in letzter Zeit mit Urin Berührung hatten. Die Konkremente entstanden sicher nicht in den Urinwegen, sondern wahrscheinlich in alten Tbc-Herden oder anderem verkalktem Gewebe.»

Der klinische Verlauf dieses Falles ist soweit von Interesse, als er deutlich den ausserordentlich schleichenden Verlauf der Urogenitaltuberkulose zeigt. Offenbar bestand seit 1924 (Nephrektomie), ja ev. schon seit 1916 (Epididymitis) eine ulzerös-kavernöse Prostatatuberkulose mit Bildung multipler Konkremente. Die gute Abwehrlage des Pat. hielt diesen Herd isoliert bis 1949, wo der Einbruch in die Urethra erfolgte, und es erneut zu einer pos. Meerschweinchenprobe kam.

Prostatakonkremente und Verkalkungen werden röntgenologisch sicherlich zu wenig beachtet. Es ist angezeigt, sich bei jeder i. v. Urographie einen Überblick nicht nur über Nieren, Ureter und Blase, sondern auch über Prostata und Urethra zu verschaffen, sowie auch über ev. Verkalkungen in den Samenblasen, Vas deferens und den Testes. Im Verein mit der üblichen urologischen Untersuchungstechnik wird man dann wohl immer zur richtigen Diagnose kommen.

ZUSAMMENFASSUNG

Es werden multiple Urethra- und Prostatakonkremente beschrieben, die sich 26 Jahre nach Beginn einer Urogenitaltuberkulose und Lungentuberkulose klinisch bemerkbar machten. Ausserdem bestehen Verkalkungen in beiden Epididymides. Genese, Symptome, Differenzialdiagnose und Behandlung werden beschrieben. Auf die Möglichkeit einer qualitativen Röntgendiagnostik von Prostatakonkrementen wird an Hand von Beispielen eingegangen.

SUMMARY

A case is reported in which multiple urethral and prostatic concrements coexisted with calcifications in both epididymides and produced clinical symptoms twenty-six years after the diagnosis of an urogenital and pulmonary tuberculosis. The etiology, the symptoms, the differential diagnosis and the treatment of these concrements as well as the possibility of determining the nature of prostatic concrements with the aid of radiography are discussed on the basis of some illustrative cases.

RÉSUMÉ

Description de multiples concrétions de l'urètre et de la prostate qui se sont manifestées en clinique 26 ans après l'apparition d'une tuberculose urogénitale et pulmonaire. Outre cela il y avait des calcifications dans les épididymes. Description de la pathogénie, des symptômes, du diagnostic et du traitement. En s'appuyant sur des cas de concrétions l'auteur tâche de définir la possibilité d'un diagnostic radiologique qualificatif.

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FROM THE INSTITUTE OF RADIOLOGY (DIRECTOR: PROFESSOR ARCANGELO VESPIGNANI), OSPEDALI CIVILI RIUNITI, VENICE, ITALY.

THE ROENTGEN RETICULAR APPEARANCE OF THE PERIRENAL FAT TISSUE IN EXTRAPERITONEAL PNEUMOABDOMEN (RETROPNEUMOPERITONEUM) AND TOMOGRAPHY[1]

by

Luigi Vespignani

The new method of gas insufflation into the extraperitoneal spaces by means of precoccygeal injection (retropneumoperitoneum) is considerably used today particularly in the Latin countries (Ruiz Rivas, Puigvert Gorro & Moya Prats, Alvarez & Mosca, Calzaretto, Juri, De Gennes, May, Simon & Herremann, Benhamou, Viallet & Chevrot, Kleimberg). Many authors in Italy have dealt with this subject and have published papers on it (Baccaglini, Bonomini, Scarinci, Neumayer, Macarini & Oliva, Sansone & De Maestri, De Giuli & Righini, Giachini, Grilli, Zattera, Salvini & Gionco, Bernardini & Salvati, Dell'Adami & Meneghini).

The first results obtained in our Institute by the employment of the extraperitoneal pneumoabdomen (we prefer this expression suggested by Romani to that of retropneumoperitoneum used by the French authors) have been the object of a previous paper in collaboration with Dr. Zennaro. In this communication some details of the technique were first given; these referred to the ways of controlling radioscopically the diffusion of the gas (oxygen) and to the necessity of taking roentgenograms both in the horizontal (prone and supine) and upright positions (frontal, lateral and oblique). Radiological films of renal pathology, controlled by surgical findings, were presented and the importance of the extra-peritoneal pneumoabdomen in the demonstration of the congenital hypoplastic kidney was emphasized. In our opinion tomography is of

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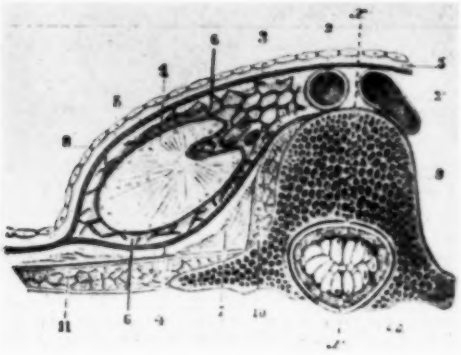

Fig. 1. A diagrammatic transverse section of the renal fascia showing (6) the perirenal fatty tissue in the form of a reticulum. (From TESTUT.)

great value in connection with pneumoabdomen. The tomography should be carried out both in the frontal and lateral planes; the latter is most likely to show the situation of renal tumours.

In the Institute of Radiology of the Ospedali Civili Riuniti of Venice the examination by means of extraperitoneal pneumoabdomen has already come into routine use. The technique is simple and is carried out by the radiologist; no harmful effects have been observed.

A new method of investigation may often be used before all its normal aspects and variations have been fully appreciated. We therefore think it justifiable to discuss the significance of certain structures frequently seen in normal cases. These consist of a reticular formation surrounding radiolucent polygonal or ovoid areolae of a diameter of 4—5 mm. They are either superposed upon the renal shadow or situated on its borders in the clear space determined by the presence of the gas in the kidney bed (figs. 2—6).

The degree of reticulation varies in different cases: it may be seen faintly even in ordinary roentgenograms but it is better shown by means of tomography. The reticulum appears to correspond to the renal bed, which suggests that it may be an anatomical constitution of the bed itself.

It is known that the »fascia propria» (originating from the thickening of the retroperitoneal connective tissue) divides at the lateral border of the kidney and embraces the organ in two layers, the prerenal and the retrorenal (viz. Zuckerkandl's fascia), together forming the perirenal fascia (fig. 1).

The kidney does not lie free in the fibrous fascia: numerous connective fibres link the external renal surface to the internal surface of the perirenal fascia. This connection tissue, loose and frail, but very abundant, particularly between the 8th—10th years of life, grows rich in fat, »gets fat» (according to Testut) and is transformed into the renal fatty capsule.

Perirenal fat varies in quantity in different subjects: it is scanty or almost lacking on the anterior surface of the kidney; it lies in a thick

Fig. 2. Extraperitoneal pneumoabdomen. Tomography of right kidney at 4 cm from the back. Note clear visualization of perirenal fatty tissue at the superior pole of the kidney.

Fig. 3. Same case. Tomogram at 10 cm from the back. A few areolae are seen at the superior pole of the kidney.

layer (2—3 cm on the average) on the posterior surface especially at the level of the poles (particularly around the inferior pole).

If we compare the formation of the perirenal fatty tissue, consisting of connective tissue containing fatty elements in its structure (figs. 1—6), with the morphology and situation of the reticular appearances seen in tomograms, we recognize their analogy.

The connective fibres of the fatty tissues are believed to correspond to the strands of the »roentgenological reticulum», while the fat lobules correspond to the clear polygonal areolae.

The physical prerequisites for roentgenological contrast are determined by the gas which has penetrated into the perirenal space and infiltrated into the structure of the fatty tissue.

In order to explain more exactly the genesis of the reticular appearances we should accept the fact that the radiolucent areolae are determined by the gaseous medium. The gas — under a degree of pressure — spreads out on the surface or other planes of the fatty capsule, and compresses the fatty lobules held in position by the connective

Fig. 4. Case II: Extraperitoneal pneumoabdomen. Tomography of right kidney at 7 cm. Reticular formation showing irregular areolae.

strands, so as to cause the radiolucent areolar reticulum. The most opaque reticulum are formed by the less yielding connective strands and the clear areolae by the fat of lower specific gravity and the interposition of a certain amount of gas among the connective strands.

The roentgenological appearances of the fatty tissue are obviously influenced by the technical factors: this explains the varying distribution of the reticulum in different cases with the same intrinsic morphology. The degree of reticulation is influenced by the amount of separation of the renal fascia due partly to the consistency of the fat tissue and partly to the quantity of the oxygen present in the perirenal spaces. How the reticulation will appear on the film is also due to the depth of the tomographic sections.

The following cases may demonstrate the typical roentgenological appearance of the reticulation.

Fig. 2 and fig. 3 show pneumo-tomograms of the right kidney of a stout 39-year-old woman: in the tomogram taken at 4 cm from the skin posteriorly, the renal fascia, the posterior portion of which is shown, appears well-outlined by gas. Only the superior pole of the kidney is visualized (owing to the obliquity of its longitudinal axis): the homo-

Fig. 5. Case III: Extraperitoneal pneumoabdomen. Tomography of right kidney showing a large mass at the lower pole of the kidney. (Surgically confirmed.) Note the typical reticular appearance of the fat tissue.

Fig. 6. Case IV: Extraperitoneal pneumoabdomen. Tomography of the left kidney. Marginal fat tissue more evident on the medial border of the kidney. Should not be mistaken for perinephritic adhesions.

geneous and regularly stranded fatty reticulum is almost completely superposed. In the tomogram obtained 10 cm from the skin posteriorly (fig. 3) the reticular structure in the region of the superior pole is barely visible.

The next case is of a man 30 years of age. The fat tissue, with similar characters to those of the preceding case is seen in the tomogram (7 cm) of the right kidney (fig. 4) — the elements of the reticulum show only slight differentiation.

Fig. 5 is of a tumour of the right kidney examined by tomography and extraperitoneal pneumoabdomen. In the tomogram (7 cm) there appears to be a considerable enlargement of the inferior pole (surgically confirmed): the fat elements are clearly seen and are arranged near the convex border of the kidney (between the middle and lower thirds).

In the last case of a man, 56 years of age (fig. 6 — left kidney-tomo-

gram — 7 cm) the trabeculation is slightly differently situated than in the preceding cases. The reticulum, instead of being superposed upon the renal shadow, occupies the clear space between the kidney and the renal fascia and is particularly prominent upon the medial border and at the inferior pole. It is important to know that the reticulation in some cases has this appearance.

The value of the appreciation of the sign of reticulation is obvious: in fact when the reticulum is marginal (as is the case in fig. 6) we should not ascribe a pathological significance to it, and should not interpret it as being in the nature of connective laminae due to perinephritis.

SUMMARY

The author describes the roentgen appearances of the perirenal fat tissue seen when extraperitoneal pneumoabdomen (retropneumoperitoneum) examinations are combined with tomography. The practical importance of the signs particularly in as much as they cause mistakes in diagnosis is emphasized.

ZUSAMMENFASSUNG

Verf. berichtet über das Röntgenbild des perirenalen Fettgewebes, welches durch die Kombination vom Retropneumoperitoneum mit der Tomographie zum Vorschein kommt. Es ist notwendig, dieses Bild zu kennen, damit das retikuläre Fettgewebe nicht irrtümlich für perinephritische Adhäsionen genehmen werden soll.

RÉSUMÉ

L'auteur décrit l'image du tissu adipeux périrénal obtenue par l'association de la tomographie avec rétropneumopéritoine. Il est nécessaire de connaître cette image pour éviter de diagnostiquer le tissu adipeux périrenal comme adhérences périnéphrétiques.

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FROM KING FAROUK 1ST UNIVERSITY, FACULTY OF MEDICINE, ALEXANDRIA, EGYPT.

THE PSEUDO-CYSTIC TRIANGLE IN THE NORMAL OS CALCIS[1]

by

Aly Sirry

Anatomy

The calcaneus is the largest bone of the tarsus. Its main part is termed the body, the posterior enlarged extremity of which forms the tuberosity and projects backwards behind the other bones of the foot. On its under surface are two projections, the medial and lateral processes. Seen from above three articular surfaces are evident, the posterior, the middle and the anterior which articulate with the talus; the posterior surface is the largest and is convex, the other two being slightly concave. Between the middle and posterior articular surfaces lies the calcaneus groove which is more or less open laterally and with the sulcus tali forms the sinus tarsi; it lodges the powerful interosseous ligaments and the nutrient vessels to both the os calcis and os talus.

The os calcaneus is a bone of the simplest structure. It is almost entirely spongy and is enclosed within a thin layer of compact bone, the cortex. The trabeculae and plates of the spongy substance, which are for the most part slender and thin, are not altogether irregular in their arrangement but are influenced to a large extent both in their structure and in their arrangement by pressure on the one hand and by the pull of the muscles on the other. The small red marrow cavities sometimes communicate with the surrounding cavities which contain the yellow marrow. In a certain percentage of cases, the bone trabeculae are so arranged and enclose these two types of cavities in such a way that a cyst-like area, almost triangular in shape, may be observed in a lateral radiograph. The lamellar structure of the bone is always clearly visible, the lamellae being regularly arranged and if this regularity of lamellation be disturbed as a result of trauma, the pattern is permanently deformed and gives what may be the only clue to an old healed fracture.

There are three main bundles of lamellar striae present in the bone which may be distinguished in the lateral projection:

1. One bundle arising from the posterior calcanean facet and spreading out fanwise to end at the posterior surface and adjacent part of the inferior surface. This is the most prominent bundle.

2. A system of curved striae arising from the anterior half of the inferior surface and sweeping backwards and upwards, diverging somewhat posteriorly to end on the

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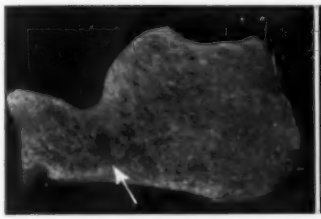

Fig. 1. Sagittal longitudinal section showing bone marrow cavity.

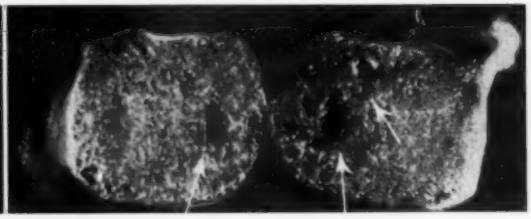

Fig. 2. Coronal section showing bone marrow cavities.

posterior surface. This system cuts across the first series at right angles in the posterior half of the bone.

3. A smaller less defined, fan-shaped system, arising from the anterior astragalar facet which spreads out, forwards and downwards, to the cuboid surface.

The first and third systems consist of pressure striae, downward continuations of vertical striae of the astragalus, and the second of tension striae.

During routine roentgen examinations of the os calcaneus a triangular, relatively translucent area, the apex directed towards the superior surface of the bone with the base resting on its inferior surface, may be observed in the films obtained true laterally. The outline of this triangular area is found to be well-defined in most of the cases; the degree of translucency of the area compared to the surrounding bone is most marked while its size relative to the size of the bone is variable. The area is not completely devoid of lamellar pattern. In some of the more striking cases, it may resemble a bone cyst and thus cause an error in diagnosis. A study of a material of 1,200 lateral radiographs of the os calcis has shown that this triangular area has a somewhat varying appearance and that it is possible to distinguish three main groups.

1. The triangular area does not show well (850 cases *i. e.* 70.8 %).
2. The area shows moderately well (265 cases 22.1 %).
3. The rest of the cases, *i. e.* 85 cases in which the area shows itself strikingly well (7.1 %). Fig. 4 is a representative case of Group I; fig. 5 a case of Group II and fig. 6 a case of Group III.

Discussion

A roentgen examination of the os calcis in the lateral plane demonstrated a triangular area which was markedly translucent and situated near the centre of the bone with its apex directed upwards, in 7.1 % of the cases of this material. It might easily have been mistaken for a bone cyst. It was in fact nothing but an area of normal bone, with a special lamellar arrangement of the spongiosa due to muscular

Fig. 3. Radiograph of anatomy specimen.

Fig. 4. Triangular area type I (arrows).

and fibrous lines of force and to attachements. The presence of red-marrow and yellow-marrow cavities also explained to a great extent its presence.

The differential diagnosis of such an area from a solitary bone cyst is made by bearing in mind that the latter appears as a clear, translucent and not necessarily round or triangular area in the bone with thinning and expansion of the surrounding cortex; if large it is usually multilocular as revealed by the presence of septa. Cysts may be multiple and a multilocular appearance may be produced by the fusion of several cysts or from the division of a single cyst by septa.

Another type of bone cyst is the fibromatous cyst, so-called chronic fibrous osteomyelitis, which appears as a small localised collection of fibrous tissue often surrounded by a capsule of sclerosed bone. In this respect it resembles roentgenologically a Brodie's abscess or a simple bone cyst. Hydatid cysts in bones mainly affect the long bones usually near the epiphyseal lines.

In the pseudo-cystic condition the translucent triangular area is trabeculated, the cortex is not ballooned and there are no loculi. It is seen at any age and there is no history of trauma or infection.

Degenerative areas in bone having the appearance of cysts while not really of a cystic nature, are seen in cases of osteitis deformans. The roentgen picture is of translucent areas simulating cysts in the bone which is itself broadened, thinned and expanded; the cortex is intact. The changes are mainly due to resorption of bone and if watched, will be seen to develop differently from cysts; the areas tend to fill up with course trabeculae of bone.

The differential diagnosis between the pseudo-cystic triangle and bone fibrosis should not present difficulties. The fibrosis may present all the appearances of a large cyst with a central translucent area, a

Fig. 5. Triangular area type II (arrows).

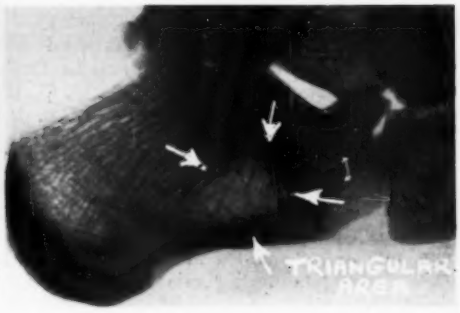

Fig. 6. Triangular area type III (arrows).

thinned overlying cortical expansion together with possible bowing or fracture.

Cysts, however, may start in the fibrous tissue from liquefactive degeneration. A fibrous mass in the bone and a bone cyst of equal translucency may produce difficulties in differential diagnosis, but generally speaking a bone cyst is more localised and may fracture easily, while in fibrosis of bone the area of translucency is more generalised and bowing or fractures may or may not take place. The term fibrocystic disease was previously used and denoted that the translucent areas were due to fibrous replacement rather than to cyst formation. The normal pseudo-cystic finding may show a central translucent area but the cortex is neither thinned nor ballooned and the bone is not bowed or fractured.

The differential diagnosis may be summarized as follows.

The pseudo-cystic triangle may be differentiated (1) from simple bone cyst by the absence of bone expansion, of expansion of the cortex, of fracture, of the history of trauma and of multi-loculation, (2) from fibrosis of bone in that the cortex of the bone is neither thinned nor expanded and that the bone never becomes bowed or fractured; the picture is not that of a fibrous mass in bone, (3) from osteitis deformans in that the trabeculations are regular and not coarse and there are no symptoms, (4) from medullary ecchondroma in the presence of normal bone lamellation and the absence of secondary bone changes and liquefaction, (5) from an arthritic cyst, that it is not in relation to a joint, (6) from hydatid cyst by the absence of caseous debris, of soft tissue changes, of fractures and by the intact lamellation and periosteum, (7) from chronic fibrous osteomyelitis by the absence of a reactive capsule of bone sclerosis surrounding the area of bone translucency and by the presence of normal lamellation in the area.

Acknowledgements

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SUMMARY

Lateral radiograms of the os calcis revealed a triangular translucent area situated near its centre. In a material of 1,200 cases it was strikingly well-defined in 7.1 % of cases, moderately defined in 22.1 % and faintly defined in 70.8 % of cases.

The differential diagnosis from pathologic changes with cyst-like appearance is briefly discussed.

ZUSAMMENFASSUNG

Bei seitlichen Röntgenaufnahmen des Os calcis fand man ein triangulăres sehr dünnes Gebiet in der Nähe der Mitte. In einem Material von 1,200 Fällen war es in 7.1 % der Fälle völlig ausgebildet, in 22.1 % mässig und in 70.8 % nur wenig sichtbar.

Die Differentialdiagnose gegenüber patologischen Veränderungen mit zystenähnlichem Aussehen wird kurz diskutiert.

RÉSUMÉ

Les radiographies latérales de l'os du talon révèlent vers le centre de celui-ci une aire triangulaire translucide. Sur un matériel comprenant 1,200 cas elle était nettement délimitée dans 7.1 % des cas, elle l'était à peu près dans 22.1 % et faiblement dans 70.8 % des cas.

La différence entre cette aire et les altérations pathologiques d'aspect kysteux est brièvement discutée.

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FROM THE ROENTGEN DEPARTMENT (DIRECTOR: PROFESSOR TORLEIF DALE), THE UNIVERSITY HOSPITAL, OSLO, NORWAY.

ASYMMETRY AND SKELETAL MATURATION[1]

by

Johan Torgersen

In the textbook of Roentgen Diagnostics by SCHINZ, BAENSCH, FRIEDL and UEHLINGER the statement is found that if there be any difference in the stage of ossification of the bones of the wrist between the two sides of the body, the left hand is generally more advanced than the right. Considering the importance in the processes in growth and maturation of this observation some data obtained during a study of the ossification of the wrist may be of interest.

Material

The data concern differences between the two sides in the number of centres which have appeared, other signs of maturation not being considered. For this reason the differences are particularly evident in the age groups in which the centres are about to appear. In 404 children below 9 years of age the right side was most advanced as to maturation in 60 cases, the left in 95 cases whereas no difference could be established in 249 cases. The difference between the two sides is significant. Thus the data confirm the statement in the textbook. The differences are too small to be a source of error in the determination of the developmental status.

A symmetrical short diaphysis of the second phalanx on the fifth finger was found in not a few individuals without any signs of mongolism. The material was divided into two groups, a diaphysis of the second phalanx smaller than one half of the diaphysis of the first phalanx being used as an arbitrary limit. In 20 individuals below 1 year of age with a short middle phalanx according to this standard, a retarded appearance of the bony centres of the wrist was found in 10 cases. In 80 individuals of the same age with no shortening of the middle phalanx a retarded maturation according to the same standards was found in 6 cases.

[1] Submitted for publication, June 18, 1951.

Comment

The latter finding shows that factors affecting the growth of a part of a limb influence the maturation of the bones of the wrist. As known the limb is found to be shorter in some types of brachyphalangy and in not a few cases the growth of the entire individual is retarded. These observations demonstrate that the rate of growth and maturation depend on local as well as on general factors. The effect of these two groups of factors, which may be both hereditary and environmental, is in many cases intermingled.

Among local factors, those affecting the blood supply may produce remarkable asymmetries, as seen in cases of infection in which the centres tend to increase in size due to hyperaemia. If, on the other hand, an infection takes place at the critical stage when the cartilage is about to be invaded by vessels no ossification at all may take place. In this way asymmetries may be produced in the sequence of the appearance of the centres.

Among the general factors, one has to distinguish between growth and maturation which partly are opposed to each other. This is particularly evident in precocious puberty, in which growth comes to an early end due to the rapidly proceeding maturation. Endocrine factors may produce differences between the right and left sides if one assumes differences regarding reactivity to hormones, a possibility which not can be excluded. Rose (1948) has shown that the maturation of the bones is accelerated in a denervated limb. The retardation of the maturation of the bones in the right wrist is probably due to a richer nerve supply on that side; also the order in which the centres appear indicates an influence of neuromuscular factors. Among the latest centres to appear are those for the navicular and the multangular bones. The epiphysis of the first metacarpal bone appears after the epiphyses of the other metacarpals. Pseudoepiphyses, which indicate slow ossification, are most frequent in the second metacarpal. The maturation proceeds more slowly in the right wrist and particularly on the radial side and in the thumb which are the most important from a functional point of view. The importance of this to the development of manual skill is evident. The right wrist and particularly the thenar side and the thumb keep the reactivity to the morphogenetic influence of functional factors for a relatively long time. The slow maturation of the skeleton which is characteristic of man as distinct from the anthropoid apes is particularly evident in the right hand which is connected with the dominant hemisphere. The slower ossification on the right side may be essential to differences in growth between the two sides of the body as well as to the asymmetrical expression of hereditary factors.

SUMMARY

The ossification of the bones of the wrist proceeds more rapidly on the left side. The reasons for this asymmetry is discussed, the main emphasis being laid on differences in innervation. The finding is considered to be of importance as regards the development of the manual skill involved in handedness, as well as regards asymmetrical growth and the asymmetrical manifestation of hereditary and environmental factors taking effect in infancy.

ZUSAMMENFASSUNG

Die Ossification der Knochen des Handgelenkes schreitet auf der linken schneller fort. Die Gründe für dieses ungleichmässige Verhalten werden besprochen, wobei der Haupt-Nachdruck auf Unterschiede in der Innervation gelegt wird. Diese Erkenntnis wird als bedeutungsvoll betrachtet einmal im Hinblick auf die Entwicklung der manuellen Geschicklichkeit und zum anderen in Hinsicht auf das asymmetrische Wachstum und auf die asymmetrische Manifestation ererbter und Umwelt-bedingter Faktoren, die in der Kindheit zur Wirkung kommen.

RÉSUMÉ

L'ossification des os du poignet s'opère plus rapidement du côté gauche que du côté droit. Les raisons de cette asymétrie sont discutées, l'intérêt principal étant porté sur les différences dans l'influx nerveux. Ces données sont considérées comme ayant de l'importance pour le développement de l'habileté manuelle au niveau du poignet et aussi pour la croissance asymétrique et pour les manifestations asymétriques héréditaires et autres facteurs similaires au cours de l'enfance.

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